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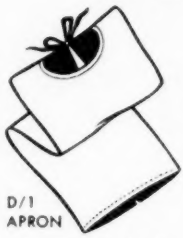

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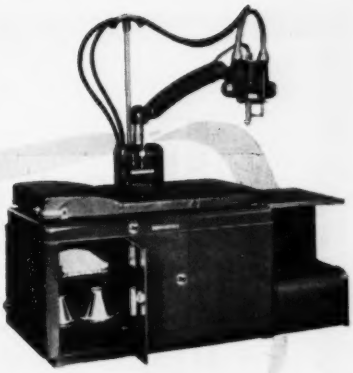

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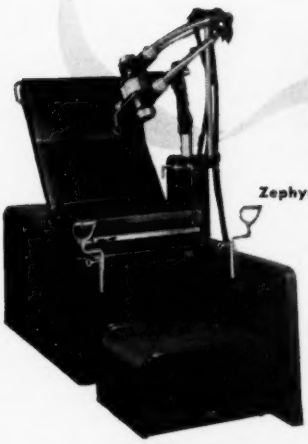

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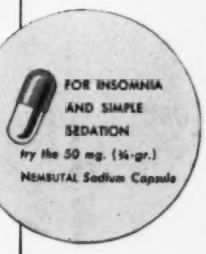

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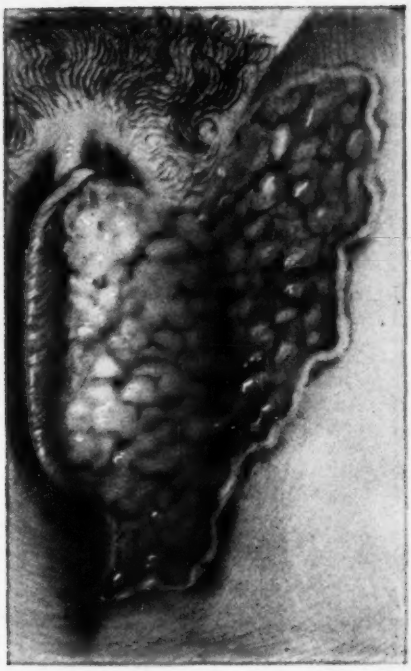

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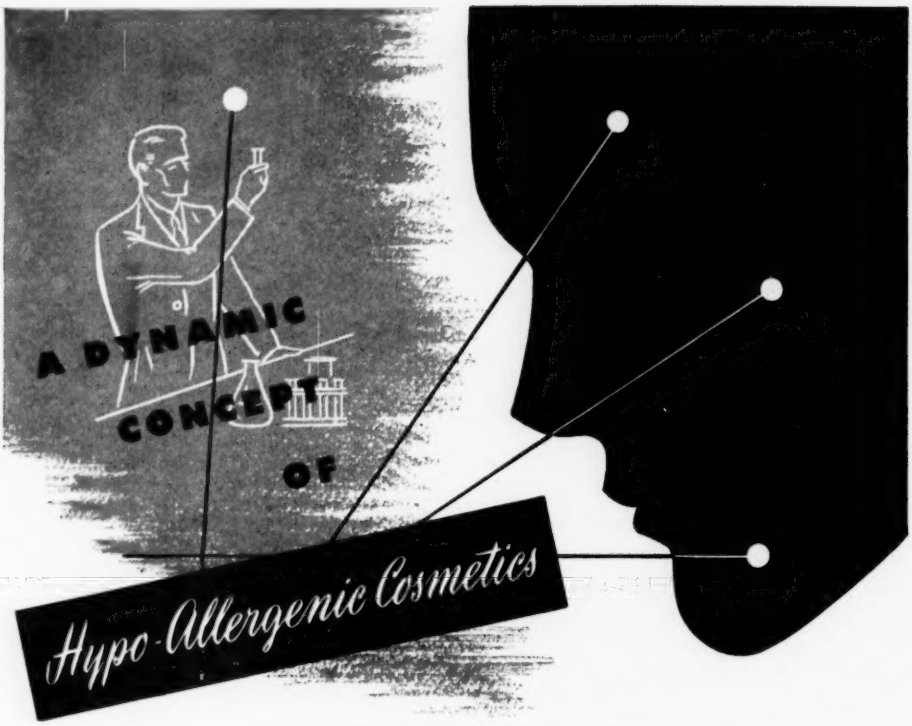

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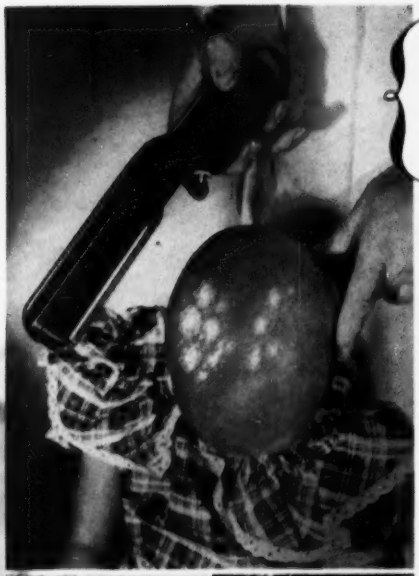

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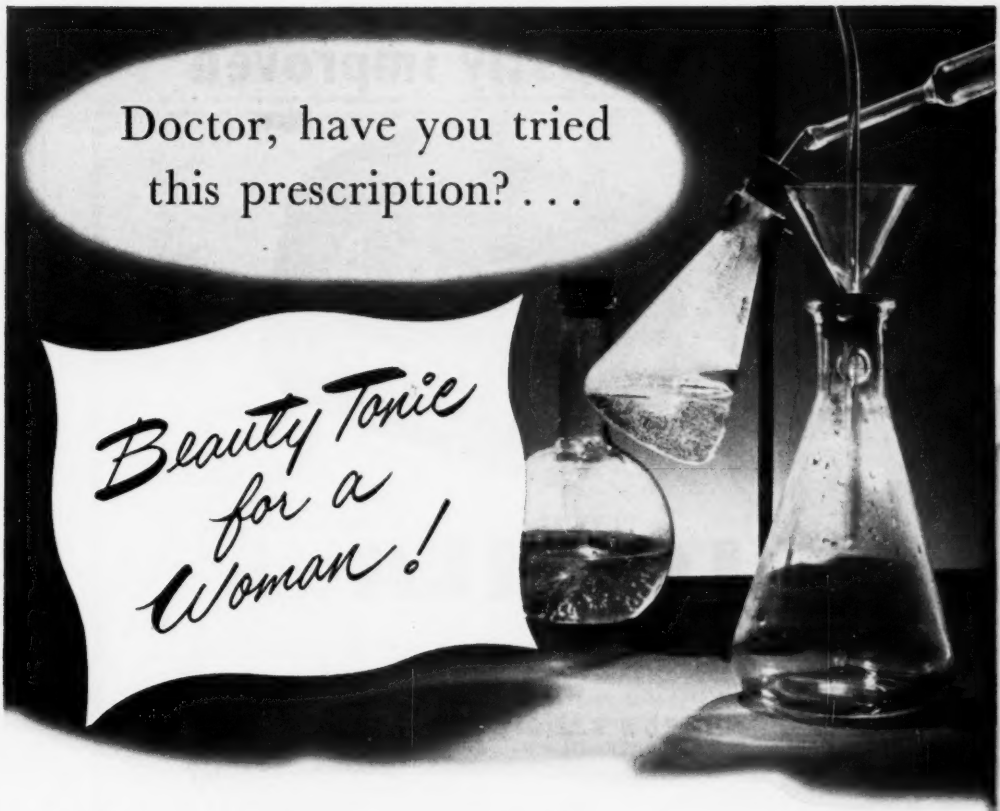

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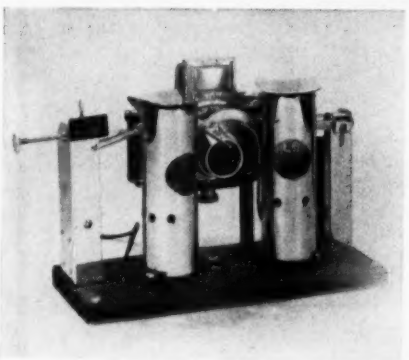

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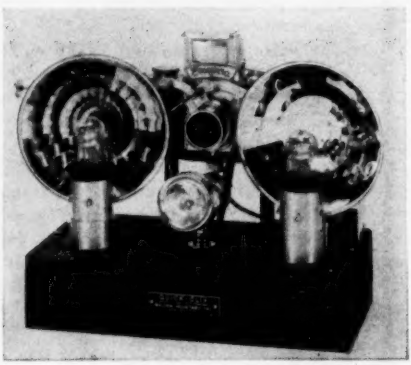

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HUMAN MELANOGENESIS: CYTOLOGY AND HISTOLOGY OF PIGMENT CELLS (MELANODENDROCYTES)

S. WILLIAM BECKER Jr., M.D.
THOMAS B. FITZPATRICK, M.D.
AND
HAMILTON MONTGOMERY, M.D.
ROCHESTER, MINN.

ALTHOUGH the presence of pigment-forming dendritic cells in the epidermis of man has been generally accepted, their origin, contour, mode of division, and role in formation of pigment have been the subject of controversy for more than a century. Bloch,[1] Peck,[2] Miescher,[3] Ormsby and Montgomery,[4] and others have assumed that the basal cells had the ability to produce melanin and that the basal cells developed dendrites following an appropriate stimulus. More recently, Masson,[5] Becker Sr.[6] and others have supported the concept that dendritic cells of the human epidermis are a specific cell type which may originate from the neural crest as do the pigment-forming cells of lower animals.

There has not been a universally accepted term for melanin-producing cells, especially those in the epidermis. It will be shown that these dendritic branched cells make up a syncytium at the level of the basal layer of cells of the epidermis. These cells are the only cells capable of forming melanin in normal human skin. We wish to suggest the term "melanodendrocyte," or "melanogenocyte," as an accurate designation of these melanin-forming cells. The term "melanoblast" was

From the Section of Dermatology and Syphilology, Mayo Clinic.

Fellows in Dermatology and Syphilology, Mayo Foundation, University of Minnesota (Dr. Becker and Dr. Fitzpatrick).

Abridgment of thesis, with additions, submitted by Dr. Becker to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology. Dr. Becker received honorable mention for an essay based on his thesis in the First Annual Essay Contest of the American Dermatological Association, 1951.

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used by Bloch to describe those cells which have the ability to form melanin in contrast to those cells which contain or phagocytize melanin and which in dermatologic literature are referred to as chromatophores and are found in the cutis, but have been referred to by some investigators as melanophores. The terms, "melanophores," "dendritic cells," "melanocytes," and "chromatophores" have been loosely used to include cells which form melanin and those which simply contain melanin. The term "melanoblast" is objectionable because in a modern cytologic sense the term "blast" is given to immature cells which differentiate into mature cells, such as erythroblasts, lymphoblasts, and leucoblasts. The pigment-forming cells in the skin are adult cells which are fully differentiated. The term "melanodendrocyte," or "melanogenocyte," is suggested as a more suitable designation for these fully differentiated cells which have the function of forming melanin. (One of us [T. B. F.] prefers the term "melanogenocyte.")

Recent findings concerning the formation of melanin and the melanodendrocytes have cast doubt on some of the previous conclusions. Bloch [1] believed that the oxidation of dopa (dihydroxyphenylalanine) by the cells of the epidermis was the work of a single specific enzyme, dopa-oxidase. This concept was always questioned because the granules of leucocytes, nerve fibrils, striated muscle cells, and certain bacteria and fungi have the ability to oxidize dopa.[7] Hesselbach and her associates [8] found evidence that dopa is oxidized by more than one enzyme in mouse melanomas; thereby further doubt was cast on the enzyme specificity of the oxidation of dopa. Lerner and Fitzpatrick [9] showed that mammalian melanomas contained the enzyme tyrosinase, and they expressed the belief that this enzyme and not dopa-oxidase was the basic enzyme in the formation of melanin. Tyrosinase has recently been demonstrated in normal human skin.[10] Nonpigmented melanodendrocytes have previously been seen in the skin of man [11] and Medawar and Billingham [12] have recently demonstrated these cells in "separated epidermis." Newer embryologic studies [13] have supported the concept that the melanodendrocytes migrate to the epidermis from the central nervous system. With these and other recent findings in mind, the cytology of melanodendrocytes in the epidermis of human beings and the formation of melanin in the epidermis were studied with the aid of histological and histochemical techniques.

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NONPIGMENTED MELANODENDROCYTES

The recent work of Medawar and Billingham [12] demonstrating the presence of nonpigmented melanodendrocytes in epidermis separated from the dermis, was repeated. The specimens utilized were nonirradiated white skin from the leg, back, arm, abdomen, and breast of males and females ranging in age from 12 to 65.

Technique of Separating Epidermis from Dermis and Staining.—The epidermis was separated from the dermis by incubating the skin in a solution consisting of 250 to 500 mg. of pancreatin in 100 cc. of Ringer-sodium bicarbonate solution at 38 C. for 10 to 15 minutes. The results were similar to those Medawar [12a] obtained by using a solution of crude trypsin. The separated epidermis was stained with dopa or gold by the technique of Medawar and Billingham, or with methylene blue as follows:

Sheets of separated epidermis were floated on a 1:2,000 solution of methylene blue (Merck) in Ringer-sodium bicarbonate solution, then floated on a cold, saturated solution of potassium ferricyanide for 5 to 20 minutes, again washed in Ringer-sodium bicarbonate solution, dehydrated in acetone for ½ minute, cleared in dimethylbenzene for 2 minutes, and mounted.

Observations.—Study of the epidermis thus treated confirmed the work of Medawar and Billingham as to the presence of nonpigmented melanodendrocytes in the human epidermis (Figs. 1, 2, and 3). No melanodendrocytes could be seen when the preparations shown in Figures 1 to 3 were examined before staining. The nonpigmented melanodendrocytes were easily stained with dopa, gold, or methylene blue. Tyrosinase activity (to be explained later), on the other hand, was completely absent in unstimulated separated epidermis. Careful examination of the stained preparations revealed that, while the melanodendrocytes were not outlined by melanin, they contained a few melanin granules. There was a direct correlation between the darkness of the skin and the number of melanin granules in the melanodendrocytes. No variation was observed in the number or shape of the melanodendrocytes in specimens of skin from different areas of the body or from patients of different ages.

Langerhans' Cell: Billingham, studying separated epidermis, found gold-impregnated dendritic cells only at the junction of the epidermis and dermis. Our study produced similar results; no gold-impregnated dendritic cells were found in the upper layers of the epidermis.

Since Langerhans' cell had been seen only in vertical preparations, further investigation was made on nonirradiated skin and on skin stimulated by ultraviolet irradiation. Gairns' [14] technique of gold impregnation used by Medawar and Billingham differs from the techniques used by Langerhans, Bloch, and Schaaf [15] only in detail; the fundamentals are the same. All of the techniques provide impregnation of the tissues with gold chloride and then reduction of the gold by physical or chemical means. For our investigation of Langerhans' cells Gairns's technique was modified slightly to enable routine embedding of tissue in paraffin.

Specimens of full thickness skin measuring 3 by 5 mm. were fixed in 10% solution of formalin for one hour. The pieces were blotted and placed in a mixture of one part of pure formic acid and three parts of filtered lemon juice and left in the dark for 30 minutes. The

14. Gairns, F. W.: A Modified Gold Chloride Method for the Demonstration of Nerve Endings, Quart. J. Micr. Sc. **74**:151-153 (Sept.) 1930.

15. Schaaf, F.: Eine Methode zur sicheren Darstellung der "Langerhansschen Zellen" in der Epidermis des Menschen, in Meerschweinchen- und Katzenpfote, Arch. Dermat. u. Syph. **176**:535-543 (April) 1938.

specimens were removed from this solution, blotted lightly, transferred to a 1% aqueous solution of gold chloride and returned to the dark for 30 minutes. (The first two steps in the Gairns gold impregnation are of only 10 minutes' duration, but the time was increased to 30 minutes so that the solutions would penetrate the partially fixed tissue.) The pieces were again blotted, transferred to a 25% aqueous solution of formic acid, and returned to the dark for 24 hours. They were then placed in Bouin's fluid for 24 hours and embedded in paraffin.

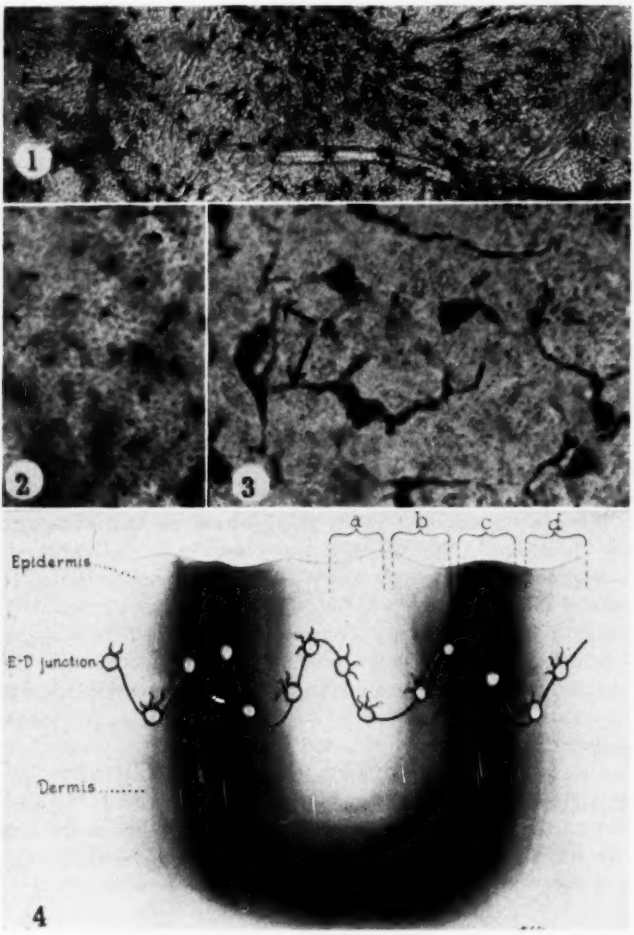

Fig. 1.—Separated epidermis from white human skin; dermal surface showing nonpigmented melanodendrocytes; dopa; × 130.

Fig. 2.—Separated epidermis from white human skin; dermal surface showing nonpigmented melanodendrocytes; gold impregnation; × 150.

Fig. 3.—Separated epidermis from white human skin; dermal surface showing nonpigmented melanodendrocytes. Arrows at *a* show two dendrites terminating on the bodies of other melanodendrocytes; arrow at *b* indicates two fusing dendrites; methylene blue; × 300.

Fig. 4.—Various zones seen in full-thickness skin impregnated with gold by Gairns' technique; *a*, zone where no gold has penetrated; *b*, zone of progressively increasing gold impregnation; *c*, purple zone where there is maximum concentration of reduced gold; *d*, zone of progressively increasing absorption of gold.

The gold chloride solution penetrates partially into the tissue, is reduced by the formic acid, and then some of the gold from the edge of the tissue is dissolved in the formic acid.

When a gold-impregnated block of tissue was bisected, four more-or-less-distinct zones were seen (Fig. 4). Histologic sections for study were taken from the junction of zones *c* and *d* where some of the gold had been dissolved.

These sections, from nonirradiated skin, contained gold-impregnated dendritic cells lying in the epidermis (Fig. 5*a*). When camera-lucida reconstructions of serial sections were superimposed, however, a dermal papilla was found to lie behind and close to these cells (Fig. 5*b*). This finding indicates that in areas where the dendritic cells appear to lie in the epidermis the surface is wrinkled and the epidermal-dermal junction is at right angles to the surface of the skin. Figure 6 illustrates the way in which folding of the skin would make the dendritic cells appear

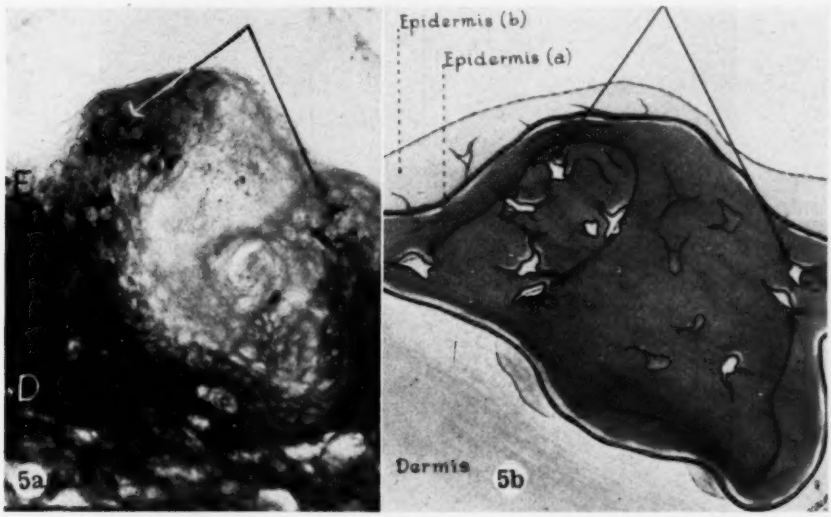

Fig. 5.—(*a*) Section of gold-impregnated skin in which the gold-impregnated dendritic cells (arrows) appear to be located high in the epidermis; × 365. (*b*) Superimposed drawings, made with the aid of camera lucida, of section shown in Figure 5*a* [*Epidermis (a)*] and the next serial section [*Epidermis (b)*]. Arrows indicate the same dendritic cells as in Figure 5*a*. In the next section, a dermal papilla is directly behind these cells, indicating that the epidermal-dermal junction was vertical in this area and that the dendritic cells seen in Figure 5*a* are actually located at the epidermal-dermal junction and not high in the epidermis.

to lie in the epidermis in a routine vertical section. The dendritic cells which lie next to the dermis in these vertical sections are difficult to identify because of intense impregnation with gold. All of the techniques of gold impregnation include as one step the immersion of the tissue in acid which causes the wrinkling and distortion.

On skin stimulated by ultraviolet irradiation the Gairns gold impregnation technique was carried out after the skin had been incubated in tyrosine. This procedure was used to insure maximal formation of melanin. The gold did not completely penetrate the epidermis, because of fixation of the tissue during incubation in tyrosine; in the deeper part of the epidermis the dendritic cells were outlined by melanin, while those close to the surface were impregnated with gold (Fig. 7).

It has been shown, therefore, that the melanodendrocytes lying at the epidermal-dermal junction may be impregnated with gold, either in preparations of separated epidermis or in routine vertical sections. Furthermore, this study demonstrates that

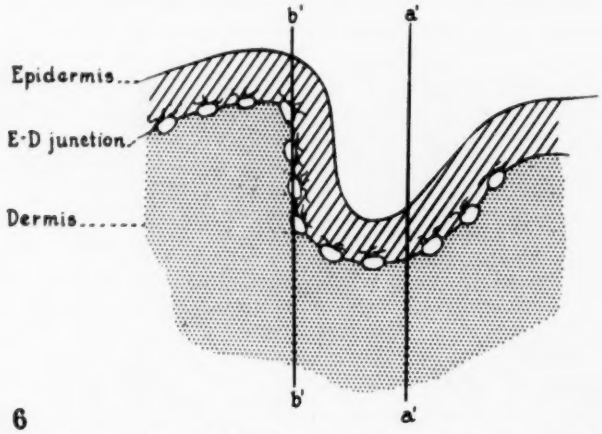

Fig. 6.—Schematic presentation of distortion possible in vertical sections when the surface of the epidermis is wrinkled; *a'-a'*, section vertically through the epidermal-dermal junction giving an undistorted section; *b'-b'*, section passing through an area where the epidermal-dermal junction is vertical. The melanodendrocytes would appear to be located within the epidermis when viewed in routine vertical section.

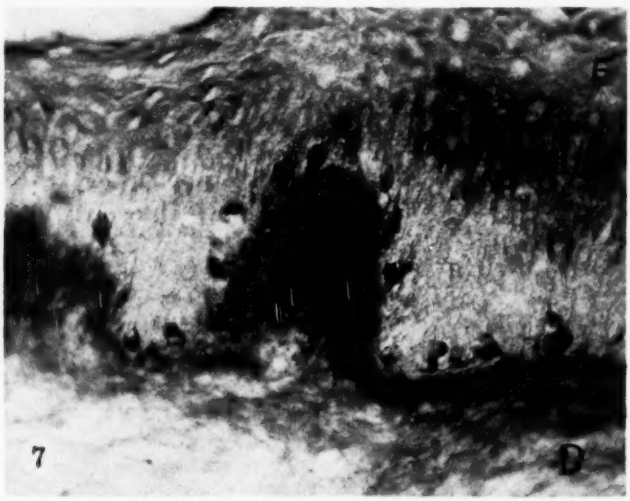

Fig. 7.—Ultraviolet-stimulated skin incubated in tyrosine and then impregnated by Gairns' technique. Melanodendrocytes at tips of the rete ridges are outlined by melanin granules, while melanodendrocytes near the surface are impregnated with gold; × 430.

Langerhans' cell is the melanodendrocyte which appears to lie in the superficial epidermis because of tissue distortion produced by the acid utilized in the gold impregnation.

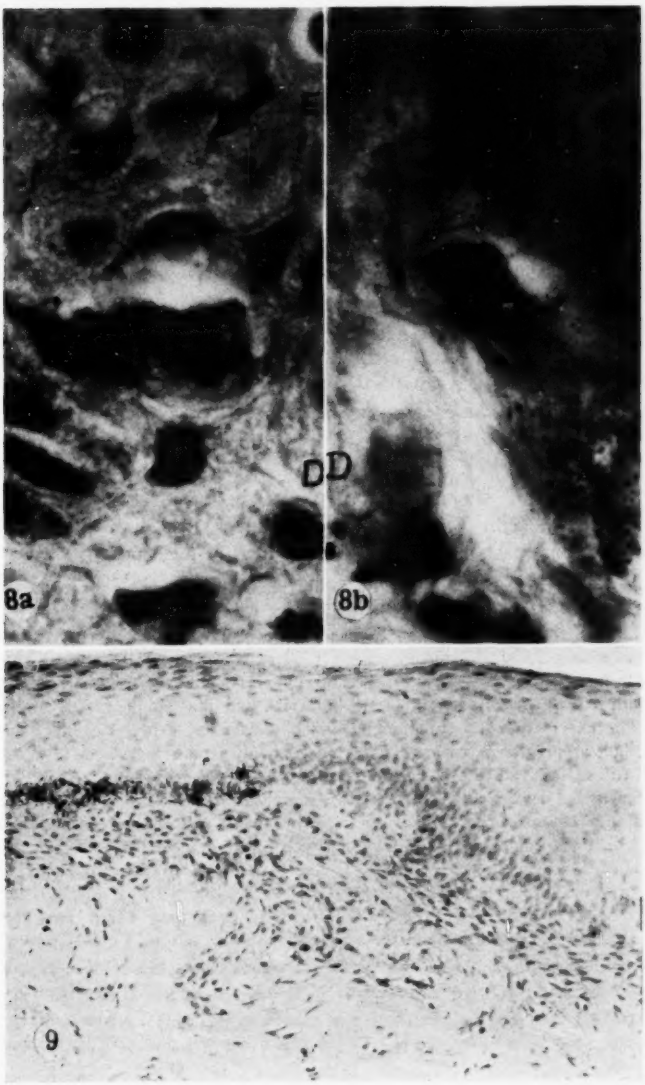

Fig. 8.—(*a*) Routine sections from axillary skin four days after ultraviolet irradiation; normal metaphase in melanodendrocytes; silver nitrate; × 1,560. (*b*) Normal metaphase in melanodendrocyte showing primary dendrite; silver nitrate; × 1,560.

Fig. 9.—Tissue from edge of a scar irradiated with ultraviolet rays for seven days. Tissue has been incubated in tyrosine, and only the melanodendrocytes have produced melanin; in the area where no melanodendrocytes have regrown, no melanin was formed; silver nitrate; × 150.

After we had demonstrated that all the gold-impregnated dendritic cells in the epidermis are melanodendrocytes, the Gairns technique of gold impregnation was used to study vitiliginous and albino skin. Vertical and horizontal preparations of gold-impregnated vitiliginous and albino skin contained the same number of melanodendrocytes as did similar preparations of normal skin. It appears, therefore, that variations in pigmentation of normal unstimulated, vitiliginous, and albino skin are due to variations in the physiologic function and not in the number of melanodendrocytes.

Mitosis in Melanodendrocytes: Billingham [12b] concluded from his preparations of separated epidermis that melanodendrocytes divided in an ameboid manner. Pinkus [16] and Masson [5] have reported finding mitotic figures in melanodendrocytes of human beings. A specimen of skin was removed from the axilla of one of us (S. W. B. Jr.) four days after a subblistering exposure to ultraviolet irradiation. The skin was incubated in tyrosine, and sections 15-μ thick were stained with silver nitrate. A careful search revealed fairly numerous mitotic figures (Fig. 8*a* and *b*). The dendrites were not withdrawn during cellular division.

CUTANEOUS MELANODENDROCYTES FOLLOWING THORIUM-X STIMULATION

Peck [2] described the changes in dopa-oxidase activity of the epidermis following stimulation with thorium X. The same stimulus was used in this study, and the changes in the tyrosinase activity and the pigment of the epidermis were observed.

Technique.—The subject is a blue-eyed, white man who has a blond coloration but who pigments readily. The anterior surfaces of the thighs, which had not been exposed to sunlight or artificial irradiation for more than five months, were used for the study. One gram of ointment, containing 2,000 electrostatic units (300 μc) of thorium X,[17] was spread evenly over a region measuring 3 by 24 cm. on the anterior part of the left thigh. The area was then sealed in with a sheet of transparent plastic material, and the ointment was left in place for five days. The exact type of emanation by which thorium X causes its effect has not been determined, but, as previously reported, infrared rays, ultraviolet rays, beta rays, gamma rays, and x-rays will all activate the enzyme tyrosinase.

All specimens for determination of tyrosinase activity were removed with a 4-mm. cutaneous punch from an area, measuring 3 by 5 cm., which showed a uniform reaction. Thin slices of skin from which the epidermis was to be separated were removed with a razor blade from various parts of the entire stimulated area. The area was cleansed with alcohol and anesthetized with a 1% procaine.

The method of measuring the tyrosinase activity was that which has recently been reported [10] and is carried out as follows:

1. The specimen removed with the cutaneous punch was placed in a 10% solution of formalin for one hour at 4 degrees C.
2. It was then bisected, and one half was placed in a 1:1,000 solution of tyrosine in a 0.1-molar phosphate buffer at pH 7.1. The other half was placed in buffer without added tyrosine.
3. Both specimens were incubated at 4 C. for 24 hours.
4. The tyrosine solution was replaced by fresh solution, and both specimens were incubated at 38 C. for 24 hours.
5. The fixation was completed in Bouin's fluid for 24 hours, and the tissue was embedded in paraffin.

16. Pinkus, H.: Mitotic Division of Human Dendritic Melanoblasts, J. Invest. Dermat. **13**:309-311 (Dec.) 1949.

17. The thorium X used in this study was supplied by Fleischman, Burd & Company, Inc., New York.

The sections for microscopic study were taken from the bisection plane so that they were from anatomically identical areas. All of the sections were cut 15-μ thick, except those stained with hematoxylin and eosin or silver nitrate after the 18th day, which were 8-μ thick. Hematoxylin and eosin, borax carmine, silver nitrate, and unstained preparations were made from each block of tissue.

Fixation was not complete at the end of one hour when the specimens were removed from formalin, and, therefore, following incubation for 48 hours, signs of separation were evident at the junction of the epidermis with the dermis. The melanodendrocytes were shrunken. This distortion was desirable, however, because the melanodendrocytes were more easily recognized when they had shrunk away from the basal cells.

The specimens of the separated epidermis studied lost their enzyme activity when fixed in formalin. The separated epidermis, therefore, was incubated without formalin fixation in the tyrosine or dopa solutions at 38 C. The incubation was limited by the disintegration of the specimen which began after about four hours. The dopa reactions were observed every 15 minutes, and the reaction was terminated as soon as the basal cells began to darken. The period of incubation in pancreatin solution necessary for the separation of the epidermis from the dermis varied with different samples of skin, and, since the incubation for 30 minutes at 38 C. markedly decreased the tyrosinase activity, these preparations could not be used to judge the change in enzyme activity. The changes in tyrosinase activity were estimated from the specimens removed by cutaneous punch, and the separated epidermis from skin, removed with a razor, was utilized to study the pigment within the dendritic cells. This was necessary because the entire dendritic cell could be seen only in separated epidermis.

The biochemistry of melanin formation has recently been reviewed.[9] It was concluded that tyrosinase was the specific enzyme concerned with formation of melanin in human skin. In this study, therefore, the conversion of tyrosine to melanin was used as the criterion of melanin-forming ability in a cell. The dopa reaction was utilized as a "stain" to outline the cells. A more detailed discussion of the occurrence and nature of the enzyme tyrosinase in human tissues will be presented in a subsequent paper.

Observations.—Gross Changes: The gross changes were similar to those observed by Peck.[2] A faint erythema was visible 18 hours after thorium X was applied. The erythema increased in intensity and had a bluish cast by the fourth day. It then began to fade and disappeared by the 12th day. Reticulated pigmentation appeared on the 5th day, became diffuse, and reached maximal intensity on the 14th to 18th day. Exfoliation began on the 15th day. The color slowly faded, and the stimulated area retained 50% of its gross pigmentation at the end of three months.

Microscopic Changes: Nonstimulated Controls from the Right Thigh: Vertical sections showed normal skin. In the basal-cell layer a few granules of melanin and clear cells were present, but no dendrites were seen. There was no increase in the amount of melanin in specimens of skin after incubation in tyrosine. Separated epidermis stained with dopa, gold, and methylene blue showed the same number of melanodendrocytes as seen in normal skin.

Specimens from the Stimulated Region: Tyrosinase Activity: The only changes from the nonstimulated control seen in the specimens taken 24 and 48 hours after stimulation by thorium X were a mild hyperkeratosis, acanthosis, and a perivascular infiltrate. Tyrosinase activity was detected in the melanodendrocytes three days after stimulation; maximal activity was present by the fifth day. Although the melanodendrocytes in subsequent preparations contained more melanin, there was never a greater difference in the amount of melanin seen in the control and tyrosine preparations on the fifth day. Tyrosinase activity remained constant until the 20th

day and then decreased until only minimal activity was present on the 32d day. Tyrosinase activity in specimens of separated epidermis roughly paralleled that seen in specimens removed by punch, but the preparations were not consistently good.

Incubation of the stimulated skin in tyrosine produced an increase in the melanin content of the melanodendrocytes only; there was no evidence of enzyme activity in the basal cells. To establish the fact that *only* melanodendrocytes form melanin, epidermis and superficial dermis were removed from an unstimulated area of the right thigh. This area was allowed to heal for 20 days and irradiated with ultraviolet rays daily for 7 days; then a specimen from within the area of the scar was removed with an 8-mm. cutaneous punch. The specimen was incubated in tyrosine and blocked in paraffin (Fig. 9). Melanodendrocytes were present in part of the specimen, and, since the entire epidermis had been removed from this area, these were new cells. A careful study of the sections revealed that these melanodendrocytes were growing back from the deeper portions of the hair follicles which had been left in the dermis. Only these melanodendrocytes had formed melanin; no melanin was present in the epidermis where there were no melanodendrocytes.

Melanin Formation: The melanin increased in the melanodendrocytes on the third day following stimulation; this was the same day that tyrosinase activity was detected. Pigment content of the melanodendrocytes increased further, and a few melanin granules appeared in the stratum corneum on the seventh day. By the 11th day, the entire stratum corneum contained melanin, but observation of separated epidermis stained with silver nitrate [18] showed that the melanodendrocytes were not yet completely outlined by melanin, and vertical sections showed no nuclear capping in the basal cells. Melanin, therefore, reached the stratum corneum before the melanodendrocytes were completely filled and before pigment was visible in the basal-cell layer. By the 14th to 18th day the melanodendrocytes in both vertical and horizontal preparations reached maximal pigmentation (Fig. 10).

One melanodendrocyte containing two nuclei was found (Fig. 11), but, since the chromosomes could not be stained, the type of division (amitotic or mitotic) could not be determined.

A careful study of the separated epidermis 14 to 18 days after stimulation (Figs. 10 and 11) revealed no pigmented basal cells. The melanin was contained in the melanodendrocyte until the stratum granulosum was reached. At this point the dendrites terminate, and free melanin granules are seen in the granular layer and stratum corneum. Vertical sections from specimens removed with a cutaneous punch on the same days (14th to 18th) contained melanin granules that appeared to be inside epidermal cells. The best explanation for these contradictory findings was that the melanin granules which appeared to be contained in epidermal cells in the vertical sections were actually within a dendrite that was cut in cross section. Since the cytoplasm of the dendrite is not stained by ordinary methods, the melanin appears to be associated with the epidermal cells. Figure 12 illustrates the way in which cross sections of dendrites would be present in the upper part of the epidermis in vertical sections.

After the 18th day, the amount of melanin within the melanodendrocytes decreased. By the 39th day no melanodendrocytes were discernible in vertical

18. Bizzozero, cited by Bloch.[1]

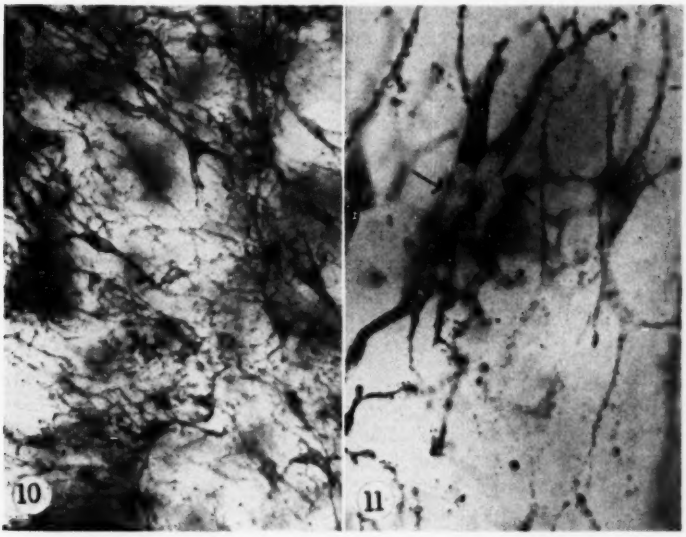

Fig. 10.—Dermal surface of separated epidermis 14 days after application of thorium X; melanodendrocytes well outlined by pigment; no basal cells outlined by melanin granules; silver nitrate; ×280.

Fig. 11.—Dermal surface of separated epidermis 14 days after thorium X was applied; melanin-filled melanodendrocyte containing two nuclei (arrows) and probably undergoing mitosis. Note the dendrites are not withdrawn; silver nitrate; × 900.

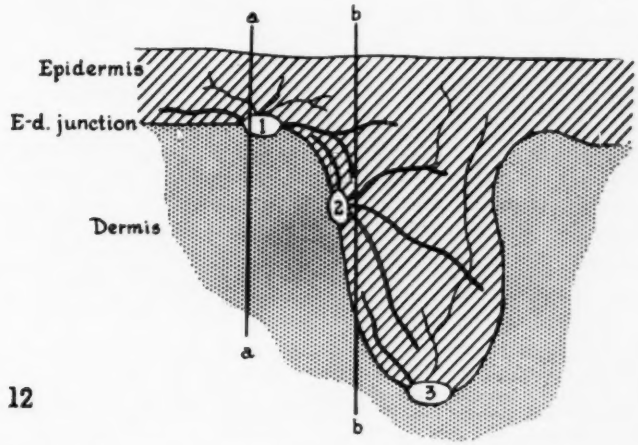

Fig. 12.—Schematic drawing showing the principal locations of the melanodendrocytes; type *1*, melanodendrocyte lying at distal end of dermal papilla sending dendrites vertically into epidermis and horizontally into adjacent rete ridge; type *2*, melanodendrocyte lying along edge of a rete ridge and sending dendrites into ridge; type *3*, melanodendrocyte lying at tip of rete ridge and sending dendrites into ridge. Vertical section cut on plane *a-a* would not sever many dendrites; section cut on plane *b-b* would contain many cross sections of dendrites lying high in the epidermis.

preparations (Fig. 13). The melanin was localized in the basal-cell layer and was assuming the form of nuclear caps. Separated epidermis removed on the same day (Fig. 14) showed that the melanodendrocytes had not changed and that they and not the basal cells contained the melanin; the melanin was present within the melano-

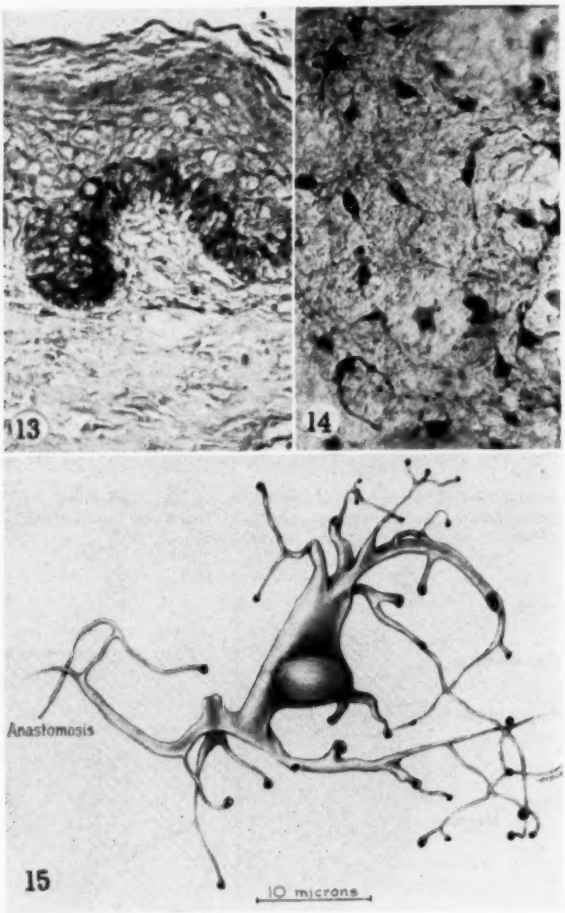

Fig. 13.—Routine section 39 days after application of thorium X; melanin is localized in the basal-cell layer, and no dendrites or melanodendrocytes are visible; silver nitrate; × 300.

Fig. 14.—Dermal surface of separated epidermis 39 days after application of thorium X; melanodendrocytes are identical with those seen in normal skin and contain melanin pigment in the form of nuclear caps; dopa; × 300.

Fig. 15.—Camera-lucida drawing of an entire melanodendrocyte from preparation pictured in Figure 14. Melanin granules were present in the form of a nuclear cap within the cell body and were also present in portions of the dendrites that were superior to basal cells.

dendrocytes and at the tips of the dendritic process in the form of "nuclear caps." Complete melanodendrocytes (Fig. 15) were drawn with the aid of a camera lucida from the preparation shown in Figure 14. These drawings illustrate the deficiencies

of the routine vertical section in studying the melanodendrocytes. The vertical section (Fig. 13) gave the impression that no melanodendrocytes were present and that the melanin was in the basal cells; separated epidermis (Fig. 14) proved that the melanodendrocytes were present and that the basal cells were not pigmented.

There appeared to be a definite increase in the number of melanodendrocytes following stimulation, but the exact numerical increase could not be accurately determined.

Chromatophores appeared at the epidermal-dermal junction on the 14th day after stimulation. These cells increased in number and migrated into the dermis. Although chromatophores were seen lying next to melanodendrocytes, there was no indication of direct passage of melanin from the melanodendrocytes to the chromatophores. It is possible (although no evidence could be found to substantiate it) that the chromatophores engulf melanin granules released by degenerating melanodendrocytes.

SUMMARY AND CONCLUSIONS

1. There has not been a universally accepted term for the melanin-forming cell in the epidermis. The term "melanodendrocyte," or "melanogenocyte," is suggested as a more suitable designation for the fully differentiated cells which have the specialized function of forming melanin pigment, rather than the older terms of "melanoblast" or "dendritic cell."

2. The finding of nonpigmented melanodendrocytes at the epidermal-dermal junction by Billingham and Medawar was confirmed. Further studies were carried out to show that the Langerhans cell is identical with the melanodendrocyte. The mode of division of the melanodendrocytes was found to be mitotic rather than amitotic or ameboid. The number of melanodendrocytes found in various specimens of normal, vitiliginous, and albino skin was constant. The variation in pigment in unstimulated vitiliginous and albino skin is due, therefore, to a variation in the physiologic function and not to the number of melanodendrocytes.

3. The melanodendrocytes were the only epidermal cells in which tyrosinase activity could be demonstrated histochemically.

4. The melanodendrocytes were the only epidermal cells which produced melanin, and this melanin appeared to be released from the dendrites in the granular cell layer rather than into the basal cells. The melanin granules associated with the prickle cells in vertical sections appeared to lie within dendrites which were cut in cross section. It appeared that the melanin granules seen as nuclear caps in the basal-cell layer were entirely within the melanodendrocytes, and it seems probable that, following stimulation, there is an almost continuous layer of melanodendrocytes at the epidermal-dermal junction.

5. Although the numbers of melanodendrocytes were constant in unstimulated skin, there appeared to be an increase in their number following stimulation with thorium X.

6. Chromatophores contained melanin at the epidermal-dermal junction, but the method of transferring the melanin from the melanodendrocytes to the chromatophores was not detected.

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CLINICAL EXPERIENCES WITH CORTISONE AND CORTICOTROPIN (ACTH) IN SOME CUTANEOUS DISEASES

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THE RESULTS obtained with steroid hormones in rheumatoid arthritis, rheumatic fever, "collagen diseases," and hypersensitivity states [1] suggested the use of these drugs in treatment of certain related dermatoses. In the following report, first a short survey of the pertinent literature is given, and then our own results in a series of cases of various dermatoses will be discussed.

SURVEY OF THE LITERATURE

Acute disseminated lupus erythematosus was first shown to be benefited by the use of corticotropin (ACTH) by Grace and Combes.[2] In 11 of 14 patients treated with cortisone or corticotropin, Baehr and Soffer, and Soffer, Levitt, and Baehr [3] obtained remissions for periods of from one to seven months with cortisone or corticotropin. However, renal changes, anemia, leucopenia, thrombocytopenia, and L. E. cells persisted, and untoward effects were frequent and sometimes

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2. Grace, A. W., and Combes, F. C.: Remission of Disseminated Lupus Erythematosus Induced by Adrenocorticotropin, Proc. Soc. Exper. Biol. & Med. **72**:563 (Dec.) 1949.

3. (*a*) Baehr, G., and Soffer, L. G.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**:229 (April) 1950. (*b*) Soffer, L. G.; Levitt, M. F., and Baehr, G.: Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus, Arch. Int. Med. **86**:558 (Oct.) 1950.

serious. Brunsting, Slocumb, and Didcoct [4] treated seven patients and obtained subsidence of arthralgia, fever, eruption, and serositis. Subjective well-being, ability to withstand stress, and "a degree of remission" occurred during treatment. Three patients died eventually of edema, infection and exhaustion, and acute hemorrhagic pancreatitis, respectively. The dose of cortisone was generally 200 mg. a day for the first few days and 100 mg. daily thereafter. Other observers included Elkinton and his associates,[1c] Thorn and others,[1b] Bordley and his co-workers,[1d] Wolfson and others,[5] Astwood and others,[6] Plotz, Blunt, and Ragan,[7] and Shy and his associates.[8] All of these authors were agreed as to the beneficial and sometimes dramatic action of corticotropin and cortisone in effecting symptomatic remissions of longer or shorter duration.

Chronic discoid lupus erythematosus was treated by Soffer and his associates [3b] (one case, details unpublished). Fromer [9] used 100 mg. of cortisone a day for four days in treating a patient with discoid lupus erythematosus of four years' duration, and there was dramatic response to this treatment, but relapse and even extension of the lesions occurred after withdrawal.

In scleroderma, Bayles and others [10] observed encouraging results in the early stages of the disease. Soffer and others [3b] and O'Leary [11] also reported on the use of steroid hormones in this disease.

Dermatomyositis responded best, as did scleroderma, when treated early (Ragan,[12] Oppel, Coker, and Milhorat,[13] Schwachman,[14] O'Leary [11]).

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4. Brunsting, L. A.; Slocumb, C. H., and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **25**:479 (Aug.) 1950.

5. Wolfson, W. Q.; Thompson, R. E.; Robinson, W. D.; Hunt, H. D.; Cohn, C.; Hayes, S. E.; Levy, R. E.; Pearlman, S. L.; Rubenstein, B. B.; Wise, W., and Zitman, J.: Physiologic and Clinical Studies with Long-Acting Preparations of Pituitary Adrenocorticotrophic Hormone, Univ. Michigan M. Bull. **16**:152 (June) 1950.

6. Astwood, E. B.; Raben, M. S.; Payne, R. W., and Cleroux, A. P.: Clinical Evaluation of Crude and Highly Purified Preparations of Corticotrophin (ACTH) Obtained in Good Yield by Simple Laboratory Procedures, Am. Soc. Clin. Invest., May 1, 1950, p. 7.

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8. Shy, G. M.; Brendler, S.; Rabinovitch, R., and McEachern, D.: Effects of Cortisone in Certain Neuromuscular Disorders, J. A. M. A. **144**:1353 (Dec. 16) 1950.

9. Fromer, J., in "Schoch Letters," Penicillin Research Center, Southwestern Medical Foundation, Dallas, Texas, November, 1950.

10. Bayles, T. B.; Stout, C. F.; Stillman, J. F., and Lever, W.: The Treatment of Scleroderma with Adrenocorticotrophic Hormone: Preliminary Observations, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

11. O'Leary, P.: In discussion at the Meeting of the American Academy of Dermatology and Syphilology, Chicago, December, 1949. Kierland, R. R., and Hines, E. A.: Cortisone and Corticotropin (ACTH) in Treatment of Scleroderma, A. M. A. Arch. Dermat. & Syph. **64**:549 (Nov.) 1951.

12. Ragan, C.: The Effect of Adrenocorticotropic Hormone (ACTH) on the Clinical Syndrome of Dermatomyositis, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

13. Oppel, T. W.; Coker, C., and Milhorat, A. T.: The Effect of Pituitary Adrenocorticotropin (ACTH) in Dermatomyositis, Ann. Int. Med. **32**:318 (Feb.) 1950.

14. Schwachman, H., in discussion on Bayles and others.[10]

Periarteritis nodosa improved strikingly on corticotropin and cortisone therapy, as reported by Baggenstoss and his associates [15] and by Goldman and his co-workers.[16]

Allergic-hypersensitivity diseases of the skin were treated by Carey and others [17] and by Howard and others.[18] These investigators used corticotropin in severe penicillin reactions, other drug eruptions, and giant urticaria. There was dramatic and complete success within 36 hours. No recurrences were seen after six days of treatment with an initial dose of 100 mg. for two days and thereafter decreasing doses of 80, 60, 40, and 20 mg. for one day each. Conn [19] reported on the case of a boy with urticaria due to food, who experienced temporary relief after receiving small amounts of corticotropin.

Howard and his associates [18] also noted rapid cure of a patient with generalized exfoliative dermatitis after a contact-type dermatitis due to iodine. A few cases of dermatitis due to atropine, sulfonamides, cinchophen, and acetylsalicylic acid were likewise treated with success by these investigators.

Atopic dermatitis (disseminate neurodermatitis) showed a complete remission in one of four patients seen by Sternberg.[20] The dose was 40 mg. daily for 10 days (corticotropin). Relapse occurred two days after the discontinuance of this therapy, but remission could again be achieved with the previous dose. Kanee and his co-workers [21] used corticotropin (25 mg. daily) with good results in a 14-month-old child with atopic dermatitis (infantile eczema) and asthma. Fromer [9] reported an inconsistent response to corticotropin in three patients with atopic dermatitis. Randolph and Rollins [22] reported two patients with atopic allergy of the skin to wheat and corn, respectively, who responded to corticotropin therapy with temporary improvement, even when the atopens were ingested. Hench and others [23] saw subsidence of a chronic neurodermatitis upon steroid therapy. Astwood and his associates [6] obtained good results in one patient with atopic dermatitis with a crude extract of pig pituitary of high potency.

15. Baggenstoss, A. H.; Shick, M., and Polley, H. F.: The Effect of Cortisone on the Lesions of Periarteritis Nodosa, Am. J. Path. **26**:709 (July) 1950.

16. Goldman, R.; Adams, W. S.; Beck, W. S.; Levi, M.; Bassett, S., and White, A.: The Effect of ACTH on One Case of Periarteritis Nodosa, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

17. Carey, R. A.; Harvey, A. M.; Howard, J. E., and Wegley, P. F.: The Effect of Adrenocorticotropic Hormone and Cortisone on Drug Hypersensitivity Reactions, Bull. Johns Hopkins Hosp. **87**:354 (Nov.) 1950.

18. Howard, J. E.; Harvey, A. M.; Carey, R. A., and Winkenwerder, W. L.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) on the Hypersensitive State, J. A. M. A. **144**:1347 (Dec. 16) 1950.

19. Conn, J. W., in discussion of Kanee, B.; Grant, J. H.; Mallek, J., and Eden, J.: ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma, Canad. M. A. J. **62**:128 (May) 1950.

20. Sternberg, T., in "Schoch Letters," Penicillin Research Center, Southwestern Medical Foundation, Dallas, Texas, August, 1950.

21. Kanee, B.; Grant, J. H. B.; Mallek, J., and Eden, J.: ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma, Canad. M. A. J. **62**:128 (May) 1950.

22. Randolph, T. G., and Rollins, J. A.: Relief of Allergic Diseases by ACTH Therapy, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

23. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of Cortisone Acetate and Pituitary ACTH in Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**:545 (April) 1950.

In psoriasis, Hench and his collaborators obtained some improvement of the skin lesions,[23] but severe eruptions of long duration did not respond completely even when high doses were administered. Thorn and his associates [1b] noted a good response in three patients. However, one patient had a relapse when therapy was stopped. Wolfson and others [5] report a patient with gout and psoriasis who responded well to "adactar" (The Armour Laboratories), a proprietary long-acting polyvinyl-corticotropin. O'Leary and others [24] discussed the case of a 25-year-old woman patient whose severe arthropathic psoriasis responded much better to corticotropin than to cortisone.

Combes and Canizares [25] treated six patients with pemphigus with cortisone. One of these patients died; three others showed essentially no improvement. In two patients, however, complete and dramatic remission occurred, and this remission was still maintained with small doses after three months. Harvey and his co-workers,[26] Ragan,[12] and Thorn and his associates [1b] also obtained good results with corticotropin in treatment of pemphigus.

In dermatitis herpetiformis Combes and Costello [27] found corticotropin "very helpful" in "some cases."

Taylor and his associates [28] observed healing of 80% of the lesions of mycosis fungoides in a 55-year-old woman patient. Relapse occurred upon withdrawal of corticotropin. Another patient showed essentially no improvement. Histologically the lesions were seen to be still active even in the improved patient. Tulipan [29] treated a 47-year-old man with eczematoid patches, infiltrated plaques, and some nodules of mycosis fungoides with 825 mg. of corticotropin in two weeks. There was some decrease in pruritus and infiltration, but one week after discontinuation of therapy relapse occurred.

In Hodgkin's disease cortisone and corticotropin were used by Pearson and Eliel,[30] Spies and his associates,[31] and Schoenbach,[32] apparently with little success. Only partial and temporary improvement was seen, and neck-gland biopsy specimens taken after the treatment showed characteristic disease changes even in a clinically regressive patient (Spies and others [31]).

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24. O'Leary, P.; Montgomery, H.; Brunsting, L. A., and Kierland, R. R.: Psoriasis: Treatment with Cortisone and ACTH, Arch. Dermat. & Syph. **62**:607 (Oct.) 1950.

25. Combes, F. C., and Canizares, O.: Pemphigus Vulgaris: A Clinicopathological Study of 100 Cases, Arch. Dermat. & Syph. **62**:786 (Dec.) 1950.

26. Harvey, A. M., and Howard, J. A.: Personal communication to J. R. Mote.

27. Combes, F. C., and Costello, M. J.: Recent Advances in Dermatologic Therapy, New York J. Med. **55**:2678 (Nov. 15) 1950.

28. Taylor, S. G.; Ayer, J. P., and Morris, R. S.: Cortical Steroids in Treatment of Cancer, J. A. M. A. **144**:1058 (Nov. 25) 1950.

29. Tulipan, L.: Failure of ACTH (Adrenocorticotropic Hormone) in the Treatment of a Case of Mycosis Fungoides, J. Invest. Dermat. **15**:349 (Nov.) 1950.

30. Pearson, O. H., and Eliel, L. P.: Use of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Lymphomas and Leukemias, J. A. M. A. **144**:1349 (Dec. 16) 1950.

31. Spies, T. A.; Lopez, G. G.; Milanes, F.; Toca, L. R.; Reborado, A., and Arenborn, M.: A Note on the Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone in the Symptoms of Leukemia and of Cortisone in Hodgkin's Disease, South. Med. J. **43**:497 (June) 1950.

32. Schoenbach, E. L.: Antineoplastic Action of ACTH and Cortisone, abstract of report read at the ACTH Adrenocortical Steroid Conference of the American Cancer Society, Oct. 28-29, 1950.

Johansen and Erickson [33] remarked about treatment of leprosy with cortisone that "early results . . . indicate that it [cortisone] may be of value in lepra reactions . . . ."

Data on Twenty-Six Patients Treated with Cortisone and Corticotropin

No.	Identification	Age	Diagnosis	Cortisone: Total Dose, Mg.	Cortisone: Length of Treatment, Days	Corticotropin: Total Dose, Mg.	Corticotropin: Length of Treatment, Days	Result	Observation After Treatment, Days	Relapse, Days After Treatment	Comment
1	1241	33	Psoriasis arthropathica	1,000	10	....	..	—	..	..	Transient improvement of mild arthritis
2	1284	34	Psoriasis arthropathica	1,000	10	....	..	—	..	..	No improvement of either psoriasis or arthritis
3	2566	37	Psoriasis vulgaris	2,000	21	....	..	—	..	..	.....
4	3080	39	Psoriasis vulgaris	2,425	20	....	..	±	..	..	Improvement
5	3711	26	Psoriasis vulgaris	3,450	23	....	..	±	..	..	Improvement
6	H. G.	28	Psoriasis vulgaris	300	3	980	11	—	..	..	.....
7	M. S.	30	Psoriasis vulgaris	....	..	1,250	11	—	..	..	"Paired comparison"; treatment with local applications and UV
8	B. S.	23	Psoriasis vulgaris	2,000	8	....	..	—	..	..	.....
9	2573	34	Penicillin urticaria	600	3	....	..	+	10	5	.....
			Penicillin urticaria	500	5	....	..	+	66	3	.....
10	2882	30	Penicillin reaction	775	6	....	..	+	23	..	.....
11	3540	24	Penicillin reaction	575	6	....	..	+	..	..	.....
12	4000	39	Penicillin reaction	775	6	....	..	+	..	..	.....
13	3456	36	Penicillin reaction	175	3	....	..	?	5	..	First asymptomatic at start of treatment
14	3288	28	Penicillin urticaria	275	6	....	..	?	3	..	First asymptomatic at start of treatment
15	D. C.	23	Urticaria due to milk	....	..	300	3	+	..	..	Relapse on milk on 3d of treatment
16	3069	23	Exudative chronic discoid and lichenoid dermatosis	2,100	20	....	..	?	..	..	Clearing possibly due to other factors (see text)
17	2712	26	Atopic dermatitis	2,000	21	....	..	+	..	..	Relapse while still on treatment
			Atopic dermatitis	2,300	67	....	..	+	..	..	On maintenance therapy
18	3418	41	Atopic dermatitis	3,900	40	....	..	+	..	..	On maintenance therapy
19	3753	25	Atopic dermatitis	3,500	23	....	..	+	..	..	Still under treatment
20	2584	40	Allergic contact-type dermatitis, generalized	2,600	28	....	..	+	..	..	Still under treatment
21	2101	31	Allergic contact-type dermatitis, generalized, exfoliative	900	9	....	..	+	10	2-3	.....
			Allergic contact-type dermatitis, generalized, exfoliative	400	4	....	..	—	..	..	Died 3 days after discontinuation of cortisone
22	1272	35	Generalized exfoliative dermatitis	2,075	17	....	..	±	90	3-4	Improvement
				2,600	20	....	..	+	..	..	Still under treatment
23	1465	53	Acute disseminated lupus erythematosus	2,000	17	....	..	+	28	18	.....
			Acute disseminated lupus erythematosus	1,325	12	....	..	—	..	..	.....
			Acute disseminated lupus erythematosus	....	..	4,752	51	+	..	..	Pronounced pituitary basophilism
			Acute disseminated lupus erythematosus	....	..	350	2	..	..	..	Died after 2 days
24	3342	48	Scleroderma	4,300	54	....	..	±	..	..	Improvement
25	1292	34	Mycosis fungoides	2,800	24	....	..	±	19	6-8	Thinning of plaques, less pruritus
26	2176	38	Alopecia universalis	2,150	25	....	..	—	..	..	Some hirsutism

33. Johansen, F. A., and Erickson, P. T.: Current Status of Therapy in Leprosy, J. A. M. A. **144**:985 (Nov. 18) 1950.

MATERIAL AND METHODS

In this series, 26 white patients were treated, 25 men and 1 woman. The age of these patients ranged from 23 to 53 years. Of the 26 patients 22 were hospitalized throughout the entire period of treatment with cortisone or corticotropin. For further details regarding these patients and their diagnoses see the accompanying table. Cortisone alone was used for 22 patients. One patient (23) received both cortisone and corticotropin in succession; another (6) was treated with the two drugs simultaneously, and two (7 and 15) had only corticotropin. For 21 patients a single course of treatment was sufficient. Four patients were re-treated once, and one patient (23) received four courses of therapy. A total of 29 courses of therapy was therefore given. The single dose of cortisone was usually 100 mg., but doses of 50 or 25 mg. were used for "tapering off" and maintenance. In the first week or 10 days, 200 mg. was usually administered daily, and in the next one to two weeks or longer, 100 mg. a day; in the maintenance phase 50 or 100 mg. every other day or only twice a week usually proved sufficient. The individual total dose varied between 175 and 4,300 mg. over a period of from 3 to 54 days. Corticotropin was administered in single doses of 12.5 to 50 mg., and the daily dose ranged from 60 to 150 mg. The lowest individual total amount was 300 mg. in 3 days, the highest, 4,752 mg. in 51 days. During therapy all patients were maintained on a low-salt diet (1,500 mg. of sodium chloride daily). Either local treatment was withheld, or only bland ointments and lotions were applied. Systemic use of drugs was avoided, particularly when a beneficial effect from these drugs could be expected.

LABORATORY STUDIES

The hospitalized patients generally were weighed daily. A slight loss in the first few days was noticed in many cases. This loss of weight was sometimes due to decrease of edema, but diminished appetite was also a factor in some cases. Edema developed only in a patient with acute disseminated lupus erythematosus (23). A few patients had elevation of temperature up to about 101 F. in the first two to three days of the treatment. In patients with primarily febrile conditions (lupus erythematosus, penicillin reactions) the temperature usually returned to normal after one to two days of therapy. Frequent blood-pressure readings showed no changes, especially no increases of any significance. The patient with lupus erythematosus maintained an average blood pressure of 170/100 mm. Hg. Chest roentgenograms were made before the start of the treatments in order to exclude pulmonary disease. Pretreatment hemograms were done routinely. In some patients a moderate leucocytosis developed in the early phase of the therapy, as shown by repeated blood counts. Absolute eosinophile counts (Thorn test) did not always disclose the expected drop in numbers. No regular correlation could be found between eosinophile response and result of therapy. Blood-chemistry studies usually showed values of about 130 mEq. per liter of Na, 4.5 mEq. per liter of K, and 95 to 105 mEq. per liter of Cl in patients receiving 1,500 mg. of NaCl a day. The patient with lupus erythematosus frequently had higher values of K (up to 5.5 mEq. per liter). In this patient there was also in the late stages of the disease a very low CO_2-combining power (as low as 16 vol.%), while normal CO_2 values were found in the other patients. Routine urinalysis, frequently repeated, did not reveal glycosuria in any patient. Albuminuria, hematuria, and cylindruria were present in the patient with lupus erythematosus. The results of special studies done in some patients do not permit reliable evaluation. Routine serologic reactions of the blood were negative for syphilis in all patients.

RESULTS OF TREATMENT

The accompanying table lists all patients and their diagnoses, the amount, duration, and result of treatment, the time of observation after treatment, and, finally, relapses and re-treatments.

Psoriasis responded poorly to cortisone. There was a partial improvement in two of eight patients. A patient with an infiltrated seborrheic type of psoriasis of 10 years' duration (4) showed almost complete regression of the lesions of the scalp and ears. However, there was little change in the lesions of the trunk and extremities. The other partial success was in a patient with an extensive but

superficial psoriasis of seven years' duration (5). In this patient a distinct paling and flattening of the eruption occurred with a considerable decrease in the scaling present. Both of these patients received relatively large doses of cortisone for long periods, namely 2,425 mg. and 3,450 mg. in 20 and 23 days, respectively. In this connection it must be mentioned that in the two patients with psoriatic arthritis the total dosage of cortisone given was low and probably inadequate. Both the arthritis and the skin lesions showed little response to cortisone therapy. The impression in general was that adrenocortical therapy was of little value in psoriasis, particularly in large, coalescent, and infiltrated plaques of long standing.

Dermatitis medicamentosa due to penicillin, in contrast to psoriasis, showed a uniformly good response to cortisone. Four patients, three of whom had serum-sickness-like reactions, improved dramatically and completely with small total doses of cortisone. Joint pains and swellings, fever, nausea, and malaise disappeared, as did the urticaria and the angioneurotic edema of the face, tongue, mouth, and throat. Two relapses occurred in one patient (9) after stopping use of cortisone. Two other cases (13 and 14) must be considered as inconclusive, as the therapy was started during what was believed to be a temporary remission of a previously severe urticaria. New lesions did not reappear after cortisone treatment was started in these two patients. Corticotropin, in doses of 100 mg. daily, successfully controlled the urticaria of a patient sensitive to milk (15). However, the urticaria recurred with a test injection of milk while the patient was still receiving corticotropin.

One patient with exudative chronic discoid and lichenoid dermatosis (Suizberger and Garbe) improved while given cortisone. However, there are so many factors involved in the reactions of these patients that it is not possible to draw any conclusions from the response of a single patient.

Good results were obtained in atopic dermatitis. All three patients in this series responded well. The lesions became pale and flat, and there was subsidence of erythema, edema, and infiltration, together with a decrease in the amount of pruritus present. Improvement occurred in the first few days. However, relapses occurred invariably and immediately after discontinuance of the cortisone. In order to keep the patients asymptomatic, an adequate maintenance dose was necessary.

In this series only two cases of allergic contact-type dermatitis were studied. In both cases the patients were treated with cortisone because of the severity of the clinical picture. In one patient (20) there was generalization of the dermatitis after repeated exacerbations due to various medicaments. The response in this patient was prompt and far-reaching. As in atopic dermatitis, there occurred paling and flattening of the inflamed skin, subsidence of edema, drying of oozing surfaces, and healing of fissures and excoriations, and the pruritus stopped almost completely.

In the second patient with allergic contact-type dermatitis, due to cyclomethycaine (surfacaine®), a generalized exfoliative erythroderma developed (21). This patient also showed a good symptomatic response to small doses of cortisone in a few days (100 mg. daily for nine days). Relapse occurred immediately after therapy was stopped, and resumption of the same treatment 10 days later effected no improvement. Peripheral circulatory collapse developed, and the patient died seven days after the start of the second course of cortisone. A detailed report on this patient will be published elsewhere. Another patient with generalized exfoli-

ative dermatitis (22) showed a moderate degree of response to cortisone. The eruption in this patient was suggestive of an underlying atopy, but seborrheic characteristics were also present. A second course of cortisone is being given to this patient at the present time, three months after the first treatment. The response at present seems satisfactory.

Four other skin diseases, one patient each, were treated with cortisone and corticotropin. In a 53-year-old white man (23) his acute disseminated lupus erythematosus was, at the time of his admission to the hospital, in remission after four short courses of corticotropin and cortisone. This patient had acute systemic lupus erythematosus, of six months' duration, after more than 30 years of chronic discoid lupus erythematosus. The remission lasted for about four months, after which time increasing arthralgia, myalgia, headache, nausea, and weakness were considered to be an indication for another course of 2,000 mg. of cortisone which was given over a period of 17 days. Good clinical improvement followed. One month later the condition relapsed with an extensive rash of the back, upper chest, and shoulders, and some lesions of the face and on the ears; there were splinter hemorrhages of the finger tips. The mucosa of the mouth, tongue, and throat showed numerous painful erosions. Malaise, nausea and vomiting, moderate fever and prostration, enlargement of the heart, and progression of a chronic nephritis necessitated the administration of a total of 1,325 mg. of cortisone in 12 days, and subsequently, because of little improvement on cortisone, a total of 4,752 mg. of corticotropin in the following 51 days. The daily dose of corticotropin ranged from 60 to 150 mg., depending on the clinical status. With corticotropin treatment, the skin lesions healed, the fever subsided, and the general condition became satisfactory. For the mouth lesions which proved resistant even to this treatment, a suspension of one part of cortisone in four parts of isotonic sodium chloride solution, as used in ophthalmological diseases, was applied topically several times daily with rapid and excellent results. Despite corticotropin therapy the disease progressed, and the patient died, probably of an acute myocardial infarct. Permission for an autopsy was not obtained.

Diffuse scleroderma in a 48-year-old white man (24) was treated with cortisone. The disease, of about 10 years' duration, was only of moderate degree. Four thousand milligrams administered in 30 days effected better function of the fingers, softening of the skin of the face, and subsidence of a mild dysphagia. The patient is now receiving a maintenance dose of 50 mg. of cortisone three times a week, with no apparent progression of the disease.

A patient with mycosis fungoides (25) with numerous eczematoid and infiltrated plaques showed resolution of many of the superficial lesions and thinning and softening of the infiltration present. However, after a total dose of 2,800 mg. in 24 days, further improvement was not apparent.

In one patient (26) with a universal alopecia of six months' duration a few coarse hairs developed on the face during cortisone therapy. These hairs were of the bristly, hirsute character, as seen in pituitary basophilism. The result of therapy, after 2,150 mg. of cortisone in 25 days, must therefore be considered a failure. Hormone treatment was given in this case because of the stimulation of hair growth by adrenocortical tumors and in pituitary basophilism, and also because this patient showed an increased breakdown of adrenocortical steroids (excretion of 40 mg. of 17-ketosteroids in 1,140 cc. of urine).

SIDE-EFFECTS

Euphoria was the most frequently seen side-effect in this series of patients. Elevation of mood was almost always present, but this change corresponded, perhaps, only to the feeling of well-being on improvement. Frank euphoric behavior was noticed in 11 patients. One of these (1) was even mildly hypomanic after having only a few hundred milligrams of cortisone. Such a dosage was also usually the minimum necessary to produce euphoria, but some change of mood was recognizable in most patients after a very few days.

Some rounding of the face was visible in five patients, but a real "moon face" developed only in the patient with lupus erythematosus. It appeared that not less than 1,000 mg. of cortisone was necessary to effect rounding of the face, and much higher doses for a moon face. These changes were never visible before the second week of treatment.

Some of the skin lesions known to develop in pituitary basophilism (Albright, Behrman and Goodman)[34] became apparent in rare instances in some of our patients. Extensive atrophic striae were noticed in the patient with lupus erythematosus after high doses of corticotropin, and in one patient with atopic dermatitis (17) who had received 3,000 to 4,000 mg. of cortisone in four to five weeks.

A few acneform lesions were noticeable in one patient (26) after about 2,000 mg. of cortisone had been administered, in the third week of treatment.

Pigmentation developed in the patient with lupus erythematosus, and even in this patient the cause of the pigmentation seemed questionable, since erythematosus eruptions often pigment spontaneously on healing. This was probably the case in our patient, since the pigmentation was present only in the sites of the healed lesions. No pigmentation of visible mucosae was observed in any of the patients.

Biopsy wounds always healed more slowly than usual with cortisone therapy.[7b]

In three patients there appeared to be a hitherto unreported side-effect, namely retardation of nail growth. Obviously, because of the relatively slow rate of the normal growth of nails, a treatment period of at least five to six weeks and a correspondingly high total dose of cortisone or corticotropin were necessary before retardation of the nail growth became apparent. In the three patients the rate of growth of finger- and toe-nails was approximately one-half the normal value for these patients.

No particular side-effect was associated with any particular disease.

COMMENT

In the course of the study it became apparent that the clinical effect of cortisone and corticotropin in the treated skin diseases manifested itself almost exclusively in a reduction of the components of acute inflammation. Dermatitis of contact or atopic type, generalized or localized, urticaria, angioneurotic edema, and the two improved patients with psoriasis showed considerable decrease of hyperemia, edema, and induration; exudation, where it existed, was diminished. Similar but less marked changes occurred in scleroderma, and in the psoriatic patient who improved. There was little effect upon the degree of scaling in psoriasis.

34. Albright, F.: Cushing's Syndrome, in Harvey Lectures, 1942-1943, Baltimore, Williams & Wilkins Company, 1943. Behrman, H. T., and Goodman, J. J.: Skin Complications of Cortisone and ACTH Therapy, J. A. M. A. **144**:218 (Sept. 16) 1950.

The lichenification of atopic dermatitis, the infiltration of mycosis fungoides, scleroderma, and inveterate psoriasis did not show an appreciable improvement or alteration in character. These same failures of corticotropin and cortisone therapy in our patients have been observed by others,[35] and even where clinical improvement was apparent relapses occurred soon after cessation of the hormone therapy, and biopsies disclosed the unaltered character of the chronic infiltrate.[28]

It is possible that longer periods of treatment and higher total dosages would be more effective in chronic processes. Hench and his associates [23] and O'Leary and his co-workers [24] were able to obtain better results in psoriasis with high doses, especially of the more effective corticotropin. However, in this connection there arises the problem of untoward reactions. A partial, or even fully, developed pituitary basophilism or an upset of the normal electrolyte balance may follow high and sustained levels of corticotropin and cortisone, and these sequelae prohibit the unlimited use of these drugs; also, in systemic diseases such as lupus erythematosus certain complications remain recalcitrant or even become progressively worse (e. g. nephritis).

The limitations imposed upon the use of adrenocortical therapy of skin diseases by its dangerous sequelae are particularly important in the matter of maintenance treatments for the prevention of relapses in atopic dermatitis, generalized exfoliative dermatitis, pemphigus, dermatitis herpetiformis, lupus erythematosus, scleroderma, and others. The gravity of the disease must be weighed against the side-effects and sequelae which may occur on prolonged therapy. For these reasons the problem of maintenance is not yet solved, and the prevention of relapses in chronic diseases, is therefore, in our opinion, not yet possible. Cortisone in tablets for oral use (Freyberg [36]) and long-acting corticotropin injections ("adactar," Armour Laboratories)[5] will certainly facilitate maintenance treatment, but these preparations, if effective, must also have the same dangerous potentialities as cortisone and corticotropin.

In conclusion, cortisone and corticotropin in dermatotherapy seem particularly useful in temporarily promoting resolution of an acute inflammatory condition. This action can prolong life in a patient with acute lupus erythematosus or be lifesaving in a severe burn or in generalized exfoliative dermatitis. In less serious diseases there is possibly no other local or systemic therapy which can produce a comparable improvement in such conditions as a fulminant drug reaction, an acute dermatitis, or an acute exacerbation of a chronic eruption in as short a time as these hormones. The practical value of these drugs in the treatment of cutaneous diseases is therefore undeniable.

It should be emphasized, however, that the effect of cortisone and corticotropin is palliative and temporary in nature and directed toward the symptom complex rather than toward the fundamental disease processes present. This was clearly demonstrated by the fact that most of the patients who showed improvement with cortisone or corticotropin tended to relapse when the drug was withdrawn.

35. Tulipan.[29] Bayles and others.[10] Hench and others.[23] Randolph and Rollins.[22]

36. Freyberg, R. H.: Effectiveness of Cortisone Administered Orally, Science **112**:429 (Oct. 13) 1950.

SUMMARY

After a short review of the pertinent literature, the number and the types of patients treated in this study are discussed, the schemes of treatment with cortisone and corticotropin (ACTH) are described, and control studies are summarized.

Results of therapy with cortisone and corticotropin show that there was a good response in dermatitis medicamentosa due to penicillin (six patients). Atopic dermatitis (three patients), contact type and generalized exfoliative dermatitis (three patients), food urticaria, acute disseminated lupus erythematosus, scleroderma, and mycosis fungoides (one patient each) also responded well but only temporarily, and maintenance therapy appeared to be necessary in these diseases. Psoriasis (eight patients) did not respond to cortisone or corticotropin. One patient with universal alopecia areata was a treatment failure, and the result in a patient with exudative chronic discoid and lichenoid dermatosis (Sulzberger and Garbe) was questionable.

Frequent side-effects were noted, but except in the patient with lupus erythematosus no serious sequelae developed.

The action of cortisone and corticotropin in those diseases in which there was a good response is believed to be due to a reduction of the different components of acute inflammation.

ADDENDUM

In addition to the series of patients reported upon in this paper there are 46 additional dermatologic cases in which the patients have since been treated with 70 courses of cortisone or corticotropin. With reference to diagnoses, the total number treated was, therefore, as follows: penicillin reaction, 17; psoriasis, 12; atopic dermatitis, 10; contact-type dermatitis, 7; exfoliative dermatitis, 4; lupus erythematosus, scleroderma, lymphoblastomas, 3 each; mycosis fungoides, urticaria, herpes zoster, 2 each; erythema multiforme, dermatitis medicamentosa, dermatitis herpetiformis, pityriasis rosea, chronic exudative lichenoid and discoid dermatosis, alopecia universalis, scleroderma adultorum, Frei-test reaction, 1 each.

Patients with the following diseases were treated in the second series which had not been represented in the first group of patients: dermatitis medicamentosa, strongly positive Frei-test reaction (good response); herpes zoster, lymphoblastoma (doubtful response); erythema multiforme, pityriasis rosea, dermatitis herpetiformis, discoid lupus erythematosus, and scleroderma (negative response).

In the other diseases, in which patients had already been treated in the first series, the results agreed in general with those obtained in the earlier cases.

Like other authors, whose papers have been published in the meantime, we also wish to emphasize that stricter indications should be applied to the dermatologic use of cortisone and corticotropin. These drugs should be administered only (*a*) if they are lifesaving or life-prolonging, (*b*) to help a patient over the hump in severe acute eruptions, and (*c*) sometimes for subjective relief in self-limited conditions of short duration. They should not be used in chronic and recurrent diseases. All contraindications must always be strictly observed.

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CORTISONE AND CORTICOTROPIN IN TREATMENT OF DISEASES OF THE SKIN

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THE DELINEATION of the place of cortisone and corticotropin (ACTH) in the therapy of various skin disorders is proceeding rapidly.[1] Angioneurotic edema, drug eruptions, exfoliative dermatitis, allergic eczema, psoriasis, pemphigus, scleroderma, and dermatomyositis are among the conditions in which improvement

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1. (*a*) Cannon, B. A.; Hopkins, J. G.; Andrews, G. C.; Colfer, H. F.; Gross, P.; Nelson, C. T., and Howell, C. M.: Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Diseases of the Skin, J. A. M. A. **145**:201-206 (Jan. 27) 1951. (*b*) Spies, T. D., and Stone, R. E.: Effect of Local Application of Synthetic Cortisone Acetate on Lesions of Iritis and Uveitis, of Allergic Dermatitis, and of Psoriasis, South. M. J. **43**:871-874 (Oct.) 1950. (*c*) Howard, J. E.; Harvey, A. M.; Carey, R. H., and Winkenwerder, W. L.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) on the Hypersensitive State, J. A. M. A. **144**:1347-1349 (Dec. 16) 1950. (*d*) Elkinton, J. R.; Hunt, A. D.; Godfrey, L.; McCrory, W. W.; Rogerson, A. G., and Stokes, J.: Effects of Pituitary Adrenocorticotropic Hormone Therapy, ibid. **141**:1274-1279 (Dec. 31) 1949. (*e*) Bordley, J. E.; Carey, R. A.; Harvey, A. M.; Howard, J. E.; Kattus, A. A.; Newman, E. V., and Winkenwerder, W. L.: Preliminary Observations on Effect of Adrenocorticotropic Hormone (ACTH) in Allergic Disease, Bull. Johns Hopkins Hosp. **85**:396-398 (Nov.) 1949. (*f*) Homburger, F.; Bonner, C. D., and Fishman, W. H.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in a Case of Pemphigus Foliaceus, J. Clin. Endocrinol. **10**:1591-1601 (Dec.) 1950. (*g*) Oppel, T. W.; Coker, C., and Wilhorat, A. T.: The Effect of Pituitary Adrenocorticotropin (ACTH) in Dermatomyositis, Ann. Int. Med. **32**:318-324 (Feb.) 1950. (*h*) Kanee, B.; Grant, J. H. B.; Mallek, J., and Eden, J.: ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma, Canad. M. A. J. **62**:428-431 (May) 1950. (*i*) Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783-793 (May 18); 824-834 (May 25); 865-872 (June 1) 1950. (*j*) O'Leary, P. A. Montgomery, H.; Brunsting, L. A., and Kierland, R. R.: Psoriasis: Treatment with Cortisone and ACTH, Arch. Dermat. & Syph. **62**:607-608 (Oct.) 1950. (*k*) DiGeorge, A., and Nelson, W. E.: Some Observations on the Use of Adrenocorticotropic Hormone in Atopic Dermatitis in Infancy, J. Pediat. **38**:164-168 (Feb.) 1951. (*l*) Irons, E. N.; Ayer, J. P.; Brown, R. G., and Armstrong, S. H.: ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses, J. A. M. A. **145**:861-869 (March 24) 1951. (*m*) Lever, W. F.: ACTH and Cortisone in Diseases of the Skin, New England J. Med. **245**:359-363 (Sept. 6) 1951.

has been recorded. The following report describes the results of such therapy in five cases of atopic dermatitis and in one case each of scleroderma, dermatomyositis, exfoliative arsenical dermatitis, pemphigus vulgaris, exfoliative psoriasis, dermatitis herpetiformis, discoid lupus erythematosus, and pityriasis lichenoides et varioliformis.

Each patient had received intensive conventional treatment with little or no change before cortisone or corticotropin was administered. Prior to hormone therapy, the circulating eosinophiles were enumerated by the phloxine method.[2] This determination was repeated weekly during treatment as long as the patient remained in the hospital. Specimens of skin, and, when indicated, of muscle, were excised for examination before treatment whenever the diagnosis was in doubt and during treatment in certain cases as a guide to the response to therapy.

During therapy, weight, blood pressure, fluid intake, and urine output were measured once daily and temperature, pulse rate, and respiratory rate four times each day. All patients were ambulatory. Intake of sodium chloride was restricted to approximately 2 gm. daily in most cases.

Cortisone[3] was given by intramuscular injection in eight cases, by intramuscular injections initially and by mouth subsequently in two cases, and by mouth only in two cases. It was applied topically in an ointment base in one case after a course of cortisone given intramuscularly and in another case after a course of corticotropin[4] similarly administered.

REPORT OF CASES

The Kahn blood test for syphilis elicited negative reactions in all cases. The total and differential leucocyte count, hemoglobin content, hematocrit reading, results of urinalysis, and chest roentgenogram were normal in all cases unless otherwise noted. Serial electrocardiograms, taken in the majority of the cases, were normal in all instances.

CASE 1.—*Atopic dermatitis*

J. N., a 25-year-old man, had complained for five years of a widespread red itching eruption which had undergone exacerbations and partial remissions. On his entry into the hospital, a salmon-red scaling eczematoid eruption involving the face, neck, antecubital fossae, and volar surfaces of the hands was present. Circulating eosinophiles fell from 794 to 593 per cubic millimeter four hours after intramuscular injection of corticotropin (25 mg.). After 12 days of unsuccessful topical treatment, cortisone was given in dosage of 200 mg. daily. Pruritus decreased in 12 hours; edema and erythema were markedly less in 72 hours, after which there was continued steady improvement. Circulating eosinophiles during treatment ranged from 44 to 89 per cubic millimeter. Prompt relapse occurred when cortisone treatment was discontinued after the 24th day. The response to reinstitution of treatment after four days was again dramatic, and the patient has been successfully maintained on a daily dose of 100 mg. for the past seven months.

CASE 2.—*Atopic dermatitis*

I. S., a 36-year-old man, had complained for eight years of a widespread red, itching, weeping eruption. On admission to the hospital, his skin generally was lichenified, scaly, and erythema-

2. Henneman, P. H.; Wexler, H., and Westerhaver, M. M.: A Comparison of Eosino-Acetone and Phloxine-Propylene Glycol Diluents in Eosinophil Counts, J. Lab. & Clin. Med. **34**:1017-1020 (July) 1949.

3. The preparation used was cortone® acetate, supplied by Merck & Company, Inc., Rahway, N. J.

4. The preparation used was "acthar," supplied by The Armour Laboratories, Chicago.

tous, with many small vesicles, some weeping, and excoriations. The face, neck, and flexor surfaces of the extremities were most severely involved. A biopsy indicated characteristics of atopic dermatitis. After four months of topical treatment and eight months of psychotherapy, the dermatitis was worse. Cortisone was given in dosage of 200 mg. daily, and after three days pruritus decreased; after four weeks the eruption had cleared except for thickening of the involved skin. Prompt relapse occurred when cortisone treatment was discontinued after the 44th day. The response to reinstitution of treatment was again dramatic, and the minimum maintenance dosage was determined by trial to be 200 mg. daily. After four months of cortisone therapy, acne of the face, upper arms, and anterior chest, mild rounding of the face, and generalized grayish-brown pigmentation of the involved skin developed. Eosinophiles numbered 592 per cubic millimeter before and 39 to 213 per cubic millimeter during therapy.

CASE 3.—*Atopic dermatitis*

A. D., a 27-year-old man, had complained for six years of a generalized itching, weeping skin eruption. On his admission to the hospital, an erythematous, dry, scaling, excoriated dermatitis with patches of lichenification and weeping involved the flexor surfaces of the arms and legs, the neck, and the trunk. A biopsy specimen showed characteristics of atopic dermatitis. The acute lesions responded well to soaks. After three weeks cortisone was administered in a dose of 200 mg. a day and later gradually decreased to 12.5 mg. During cortisone therapy, there was improvement of the texture of the involved skin and the patient experienced very little pruritus. Prompt relapse occurred when the administration of cortisone was stopped after 34 days.

CASE 4.—*Atopic dermatitis*

G. E., a 43-year-old man, was troubled for four months by an itching red raised eruption of both forearms, thighs, and popliteal areas. He had been given penicillin by injection three weeks before admission to the hospital. On entry, there was an erythematous thickening of the skin of the above-mentioned areas with patches of weeping excoriations. After two weeks of topical therapy, there was only slight improvement. Cortisone was given in a dosage of 200 mg. daily. After three days, the skin color was normal and pruritus ceased. There were only slight dryness and scaling of the involved skin at the end of the seven-day course of cortisone. Prompt relapse ensued three days after discontinuance of the hormone treatment.

CASE 5.—*Atopic dermatitis*

E. O., a 28-year-old man, had a recurrent, itching eruption of the dorsa of both hands for several years. Rapid spread of the eruption to both arms followed the use of proprietary ointments two weeks before he entered the hospital. On entry, the skin of the hands and forearms was edematous and erythematous, with a superimposed papulovesicular eruption and some weeping incrustations. The diagnosis of atopic dermatitis with a superimposed drug eruption was made. Subsidence of the pruritus, erythema, and edema occurred within 48 hours after the beginning of cortisone administration in the dosage of 225 mg. a day. Cortisone therapy was discontinued on the fourth day because a few urticarial lesions developed on the thighs and the patient had pruritus and erythema at one of the sites of injection. The urticaria subsided after the oral use of tripelennamine hydrochloride, and the original lesions cleared completely after local potassium permanganate soaks.

CASE 6.—*Scleroderma*

J. B., a 22-year-old man, entered the hospital with a four-year history of scleroderma confirmed by a biopsy two years before admission. On entry, there were generalized leathery thickening and tightness of the skin which were marked only about the face, neck, upper extremities, and upper trunk. Circulating eosinophiles numbered 136 per cubic millimeter. Biopsy revealed findings characteristic of scleroderma in the skin, without involvement of muscle. Cortisone was given in dosages of 200 mg. daily for 28 days and 100 mg. daily for 22 days. During therapy, there was no apparent clinical improvement, and serial biopsy specimens on the 6th, 11th, 16th, and 21st treatment days revealed no change, but one on the 49th day revealed "some decrease in the amount of perivascular infiltration but no change in the collagen tissue." Circulating eosinophiles ranged between 11 and 81 per cubic millimeter during therapy.

CASE 7.—*Dermatomyositis*

J. M., a 35-year-old man, entered the hospital with an eight months' history of fatigue with muscle soreness and a five weeks' history of edema of the arms and legs and dyspnea on exertion.

On entry, brawny edema of the fingers, hands, forearms, and lower extremities up to the midthighs was present. The spleen was palpable just below the costal margin. The muscles were not tender. Results of renal and hepatic function tests were normal. The serum albumin was 2.5 gm. and the globulin 3.1 gm. per 100 ml. A muscle biopsy revealed chronic myositis, compatible with dermatomyositis, although the skin, as not infrequently occurs, was normal. Cortisone was given initially in dosage of 200 mg. daily for 51 days. After three days, there was gradual subsidence of edema and symptoms. A muscle biopsy specimen taken after 15 days of therapy revealed a marked decrease of the lymphatic infiltration of the interstitial tissue. Relapse occurred two weeks after cessation of cortisone therapy. Response to re-treatment for 105 days was again excellent, and the patient has been successfully maintained on a daily dose of 75 mg. for the past four months. The serum albumin showed a slight increase to 3.1 gm. per 100 ml.

CASE 8.—*Arsenical dermatitis*

R. B., a 39-year-old man, entered the hospital with a diffuse exfoliative dermatitis of four weeks' duration. The eruption followed a series of neoarsphenamine injections given because of a penile ulcer (although results of serological tests for syphilis were negative). He had lost 30 lb. (13.6 kg.). Five years earlier a bullous eruption had developed after he took a sulfonamide. On entry there was a generalized florid erythema of the skin with flaky exfoliation, generalized edema, and loss of all hair from the trunk and extremities. The nails were thickened. The total leucocyte count varied from 25,000 to 6,500 per cubic millimeter, with the eosinophiles ranging from 27 to 2%. The serum total proteins varied from 2.3 to 6.7 gm. per 100 ml. The result of a biopsy was considered to be consistent with arsenical dermatitis. After six months of local and supportive treatment, the eruption was somewhat improved. Cortisone was given in dosage of 200 mg. daily initially for one week and after that in gradually decreasing doses for 43 days. The skin was vastly improved after eight days and after four weeks was normal save for a few incrusted lichenifications about the ankles. At the end of therapy, the patient was asymptomatic and remained so during five months' follow-up observation. Circulating eosinophiles numbered 1,156 per cubic millimeter before cortisone treatment and ranged from 350 to 156 per cubic millimeter during treatment.

CASE 9.—*Pemphigus vulgaris*

M. K., a 56-year-old man, was troubled for two months by blisters on the legs, thighs, forearms, and trunk. The lesions were noted to rupture and to be replaced by black incrustations. The patient had been treated for primary syphilis in 1937. On his admission to the hospital there were bullous lesions varying in size (2 mm. to 2 cm.), shape, and phase of evolution scattered over the regions noted above. Pressure on a new bulla caused extension of the contents into adjacent normal-appearing skin. The serum total proteins were 7.2 gm. per 100 ml., with 3.7 gm. of albumin and 3.5 gm. of globulin. Circulating eosinophiles numbered 213 per cubic millimeter initially and varied from 72 to 309 per cubic millimeter. A biopsy of a lesion revealed the characteristics of pemphigus vulgaris. Cortisone was given in dosage of 200 mg. daily for 36 days. Many bullae healed after three days. Only a few small new lesions appeared during treatment. Brownish-gray pigmentation was evident at the healing sites. Relapse occurred one month after discontinuance of cortisone therapy. Response to reinstitution of treatment was again excellent, and maintenance therapy has been very satisfactory (nine months).

CASE 10.—*Generalized psoriasis*

J. H., a 63-year-old man, was troubled for 30 years by a fairly typical exfoliative psoriasis involving the skin of most of the body. Various types of therapy evoked little lasting improvement. The patient became depressed, was unable to work, and had suicidal ideas. On his admission to the hospital, the skin of the entire trunk, scalp, and extremities was leathery, dry, erythematous, and exfoliating. There were raised circinate scaling red patches on the legs. Eosinophiles numbered 210 per cubic millimeter. A skin biopsy revealed characteristics of psoriasis. Three days after the start of cortisone therapy in dosage of 200 mg. daily, there was much less scaling; erythema and dryness improved in a week. Because of extreme euphoria and somewhat irrational behavior, cortisone treatment was stopped after 20 days. Within a few days there were increasing erythema and scaling. The patient retained a degree of euphoria, and, during the subsequent six months, his skin was in better condition than it had been for many months prior to cortisone therapy.

CASE 11.—*Dermatitis herpetiformis*

F. J., a 63-year-old man, was troubled for 18 months by an itching, blister-like eruption on the trunk and extremities. Initial treatment with sulfapyridine caused gradual disappearance of all lesions. Relapse ensued three weeks after the sulfapyridine treatment was stopped. Upon his resuming sulfapyridine treatment a severe generalized urticarial eruption developed. Four other sulfonamides produced the same type of urticarial eruption. On his coming to the hospital symmetrical, grouped, 0.25- to 0.50-cm. lesions were present on the extensor surfaces of the trunk and extremities. Most of the lesions were dried incrustations overlying an erythematous base. There were a few scattered new vesicles and pigmented sites of old lesions. The clinical diagnosis of dermatitis herpetiformis was so apparent that a biopsy was not performed. Circulating eosinophiles fell from 231 to 64 per cubic millimeter four hours after intramuscular

Results of Seventeen Courses of Cortisone Therapy in Thirteen Patients with Skin Disorders

Case No.	Diagnosis	Duration of Treatment, Days	Mean Daily Dose, Mg.	Route	Clinical Response	Day* Response Evident	Day† of Relapse	Comment
1	Atopic dermatitis	24	200‡	Oral	Excellent	3	3	Remission sustained with maintenance therapy
		See text	100§	Oral	Excellent			
2	Atopic dermatitis	44	170‡	I. M.‖	Good	3	3	Remission sustained with maintenance therapy
		See text	200§	I. M. and oral	Good	3	..	
3	Atopic dermatitis	34	170	I. M.	Good	7	3	.....
4	Atopic dermatitis	7	214	I. M.	Excellent	2	1	.....
5	Atopic dermatitis	4	225	I. M.	Good	2	..	Complete recovery
6	Scleroderma	50	156	I. M.	Unchanged	..	..	.....
7	Dermatomyositis	51	182	I. M.	Excellent	3	14	Remission sustained with prolonged therapy
		102	136	I. M.	Excellent	3	..	
8	Exfoliative arsenical dermatitis	44	110	I. M.	Excellent	3	..	Complete recovery
9	Pemphigus vulgaris	36	200‡	I. M.	Good	3	28	Continued improvement with maintenance therapy
		See text	104§	I. M. and oral	Good	3	..	
10	Psoriasis	20	122	I. M.	Good	3	..	Partial sustained remission
11	Dermatitis herpetiformis	..	See text	Topical	Unchanged	..	..	No effect after 13 days of ACTH and 3 day of cortisone given topically
12	Discoid lupus erythematosus	24	204	I. M. and topical	Fair	See text	..	Periphery of lesions improved
13	Pityriasis lichenoides et varioliformis	16	206	Oral	Good	16	..	Improvement continued after cortisone therapy was stopped

* Days after initial dose of cortisone.
† Days after discontinuance of cortisone therapy.
‡ First course of cortisone.
§ Second course of cortisone.
‖ Intramuscular.

injection of corticotropin (25 mg.). After 13 days of corticotropin administration (145 mg. the first day, 80 mg. the second day, and 40 mg. daily for 11 days), there was no change in the skin lesions. Cortisone ointment (0.3% in an oxycholesterol-petrolatum ointment base [aquaphor®]) was applied topically for three days without benefit.

CASE 12.—*Discoid lupus erythematosus*

O. C., a 28-year-old man, had noted in 1943 a "pimple" on his right cheek. This lesion gradually enlarged with a central depigmented area and with itching scaling at the periphery. A similar lesion developed on the inner surface of the left ear lobe. Various types of therapy were of no avail. One brother had died of "skin trouble." On his admission to the hospital, a 7- by 5-cm. lesion as described above was on the right cheek and a similar lesion involved most of the inner aspect of the left ear, both characteristic of discoid lupus erythematosus. Cortisone given in dosage of 200 mg. daily for 23 days was without effect except that hair grew on the central portion of the lesion on the cheek after 10 days. Eosinophiles ranged from 154 to 51

per cubic millimeter during therapy. After application of a 0.5% cortisone ointment twice daily for four weeks to the lesions, there was less heaping-up and pruritus at the edges of the lesions.

CASE 13.—*Pityriasis lichenoides et varioliformis*

J. C., a 29-year-old man, had complained for 10 years of a generalized "spotty, scaling" eruption. Numerous types of therapy were of no avail. On his entry into the hospital there were numerous annular circumscribed macular erythematous lesions of the skin of the trunk and extremities; scattered lesions were in a scaling or desquamating phase. Eosinophiles fell from 133 to 111 per cubic millimeter four hours after intramuscular injection of corticotropin (25 mg.). The clinical diagnosis of pityriasis lichenoides et varioliformis was confirmed by biopsy. During the course of administration of cortisone in a dosage of 200 mg. daily for 15 days, there was no apparent clinical response. However, a biopsy on the last day of treatment revealed much less inflammatory cellular exudate than was present prior to treatment. After the course of cortisone was completed, most of the skin lesions healed, leaving residual depigmentation of the skin at the sites of healing. The improvement continued during four weeks of follow-up.

COMMENT

The four patients with atopic dermatitis of long duration (Cases 1 to 4) experienced dramatic relief of symptoms, with concomitant objective improvement, within a few days after the beginning of cortisone therapy, but an abrupt exacerbation occurred within three days after treatment was discontinued. Two of these patients (Cases 1 and 2) subsequently maintained sustained improvement during continued therapy over periods of seven and five months' duration, respectively. The patient with more acute atopic dermatitis (Case 5) improved promptly during treatment, and the disease had not relapsed three months after treatment was ended. Urticarial lesions of the type which occurred in this patient have not been observed in any others. Whether these represented a delayed reaction to one of the many local preparations which had been used previously or were due to the cortisone itself or another ingredient of the suspension is not clear.

There was no clinical improvement in the patient with diffuse scleroderma. A biopsy specimen taken after 49 days of cortisone therapy showed decrease in the perivascular infiltration but no change in the collagen deposition.

The patient with dermatomyositis had an excellent clinical as well as histologic response to each of two courses of cortisone therapy of 51 and 102 days' duration, respectively. The muscle biopsy specimen obtained prior to each course of treatment showed inflammatory changes of early dermatomyositis. After each course of treatment, only muscle of normal appearance was seen. The relapse after each period of cortisone administration suggests that continual therapy is indicated in this disease, for which there is no other efficacious treatment.

The response of the patient with exfoliative arsenical dermatitis was striking. He had improved slowly during prolonged treatment prior to the administration of cortisone. When cortisone was given, there were abrupt acceleration of the healing process and remarkable relief of subjective symptoms.

The favorable response to cortisone therapy in the patient with pemphigus vulgaris is particularly impressive because of the usual fatal outcome of this disease. The course of this patient, like those reported by Cannon and co-workers [1a] and Homburger, Bonner, and Fishman,[1f] indicates that maintenance therapy is required. Although patients who die with pemphigus sometimes show degenerative changes of the adrenal cortex,[5] the favorable response of this disease to cortico-

5. Goldzieher, J. W.: The Adrenal Glands in Pemphigus Vulgaris: Report of 6 Autopsies and Review of the Literature, Arch. Dermat. & Syph. **52**:369-375 (Nov.-Dec.) 1945.

tropin therapy reported by others [1a,f] indicates that the adrenal cortex may remain responsive to stimulation by corticotropin. Indeed, we have recently observed that a patient with pemphigus who did not respond when 400 mg. of cortisone was given daily for two weeks did improve during the subsequent administration of corticotropin in large doses.

During cortisone administration the patient with exfoliative psoriasis showed remarkable improvement, which was partially maintained after treatment was discontinued.

The patient with dermatitis herpetiformis failed to respond either to parenteral administration of corticotropin or to topical application of cortisone.

There were slight changes at the periphery of the lesions of the patient with discoid lupus erythematosus and subjective relief of itching. However, further therapy did not seem warranted in view of the limited extent and benign nature of the lesions.

The patient with pityriasis lichenoides et varioliformis failed to respond clinically during treatment, although a biopsy specimen taken on the last day of therapy revealed definite changes toward normal. Striking clinical improvement became apparent during the four weeks after completion of the course of cortisone. The depigmentation of the skin at the sites of healing seen in this patient appears to be unique in our experience and that of others.

Miscellaneous Observations.—Prior to treatment, the number of circulating eosinophiles exceeded 400 per cubic millimeter in 6 of the 13 patients. In 11 of the 12 patients who were given cortisone orally or intramuscularly, the total eosinophile count decreased by 66 to 97% within one to two weeks after the start of therapy. A subsequent return of these cells toward the initial level was frequently observed, but these changes were variable and without apparent relation to the clinical response.

Mild edema of the lower legs developed in seven patients while their dietary intake of sodium was unrestricted. In all instances, the edema subsided after the intake of sodium chloride was limited to approximately 2 gm. daily. Although detailed studies of levels of serum potassium were not made on these patients, there was no clinical or electrocardiographic evidence of hypopotassemia in the patients studied. No potassium supplements were given.

Rounding of the facial contour occurred during therapy in six patients. This finding was commonest in those who received large doses over long periods. Mild or moderately severe facial acne developed in three patients. Severe acne of the face and trunk occurred in the patient with scleroderma.

A feeling of well-being was described by each of the patients during therapy. In only one instance did psychiatric symptoms of such severity occur that administration of cortisone was discontinued. Insomnia and restlessness were common complaints of all the patients. A marked increase in appetite was noted by the majority of them. Glycosuria did not develop in any of the patients.

All the effects described above disappeared after therapy was stopped. Brownish-gray pigmentation of the skin, but not of the mucous membrane, occurred in three of the patients treated for periods of three months or longer and has remained.

Delay of wound healing was seen after each biopsy specimen was taken in the patient with scleroderma, but not in any of the other seven patients from whom one or more biopsy specimens were obtained.

Marked lassitude, fatigue, and muscle weakness were noted by six patients for a few days during the first or second week following completion of a course of treatment, which in each instance had extended over a period of 24 days or more.

Dosage.—The dosage schedules employed have been varied, and doses, generally, were larger than those reported by others. There was no appreciable difference in the response of patients for whom cortisone therapy was discontinued after graduated reductions of the dose from that of others in whom the medication was stopped abruptly. The usual program at present consists in administration of 300 mg. orally in four divided doses on the first day of treatment, followed by 200 mg. daily in four divided doses. With improvement the dosage may be decreased to 100 mg. daily. How long to continue the administration of cortisone to patients who show no clinical response within a fortnight remains unsettled. It may be that serial biopsies will afford a basis on which to decide whether more prolonged treatment in indicated.

SUMMARY

Experience with the use of cortisone and corticotropin (ACTH) in the treatment of a variety of skin disorders is described.

The conditions which improved during cortisone therapy include atopic dermatitis, dermatomyositis, exfoliative arsenical dermatitis, pemphigus vulgaris, psoriasis, pityriasis lichenoides et varioliformis, and probably discoid lupus erythematosus. Maintenance cortisone therapy was required in the cases of chronic atopic dermatitis, in the case of dermatomyositis, and in the case of pemphigus vulgaris. In the one case observed, the scleroderma did not improve during a 50-day course of cortisone. In one case dermatitis herpetiformis failed to improve during a 13-day course of parenteral corticotropin administration or on topical application of corticotropin for three days.

ELECTRICAL SKIN RESISTANCE STUDIES IN TWO PERSONS WITH CONGENITAL ABSENCE OF SWEAT GLANDS

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AT PRESENT the electrical resistance of the skin is widely employed in measuring the activity of the sympathetic nervous system.[1] Its use is based on the fact that the electrical resistance offered by the body to the passage of a minute imperceptible direct current is a measure of sweat-gland activity, which in turn is controlled by the sympathetic nervous system. In this laboratory and elsewhere, the mapping of bodily areas of relatively high and low skin resistance has been used to diagnose peripheral nerve injuries, to follow the progress of nerve regeneration after nerve suture, to localize the level of lesions of the spinal cord or roots, to determine the effectiveness of sympathectomy or procaine paravertebral blocks, and to aid in determining preoperatively the desirability of sympathectomy in various peripheral vascular diseases. In addition, it has been widely used in less clinically applicable experimental work.

The present report describes the results of extensive skin resistance studies on two patients with congenital absence of sweat glands. This rare malady is known most commonly as hereditary ectodermal dysplasia of the anhidrotic type. Persons with this disease are characterized by distinguishing facies, scantiness of hair, missing and deformed teeth, and absence of sweat glands. The disease is exceedingly rare, especially in females. Lord and Wolfe[2] have tabulated 42 cases, only 2 of which involved females.

REPORT OF CASES

Mrs. M. B. was a 43-year-old Jewish woman who was first seen in 1940 at the Johns Hopkins Hospital, where she had brought her daughter because of the latter's absence of sweating and extreme heat intolerance. Mrs. B. stated that when she herself was a very young child she began to notice extreme exhaustion whenever she attempted to play vigorously with other children. Her whole life had been centered about artificial means of keeping cool in

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Henry Strong Denison Scholar for 1949-1950, 1950-1951.

From the Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital.

The work described in this paper was done under a contract between the Office of the Surgeon General of the United States Army and the Johns Hopkins University.

1. Richter, C. P., and Woodruff, B. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, Surgery **10**:957, 1941. Richter, C. P.: Cutaneous Distribution of Sympathetic Nerves Determined by the Electrical Skin Resistance Method, Tr. Am. Neurol. A. **72**:148, 1947. Ray, B. S., and Console, A. D.: Residual Sympathetic Pathways After Paravertebral Sympathectomy, J. Neurosurg. **5**:23, 1948. Thompson, J. E.; Brose, N. A., and Smithwick, R. H.: Patterns of Electrical Skin Resistance Following Sympathectomy, Arch. Surg. **60**:431 (March) 1950.

2. Lord, L. W., and Wolfe, W. D.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type (Congenital Ectodermal Defect), Arch. Dermat. & Syph. **38**:893 (Dec.) 1938.

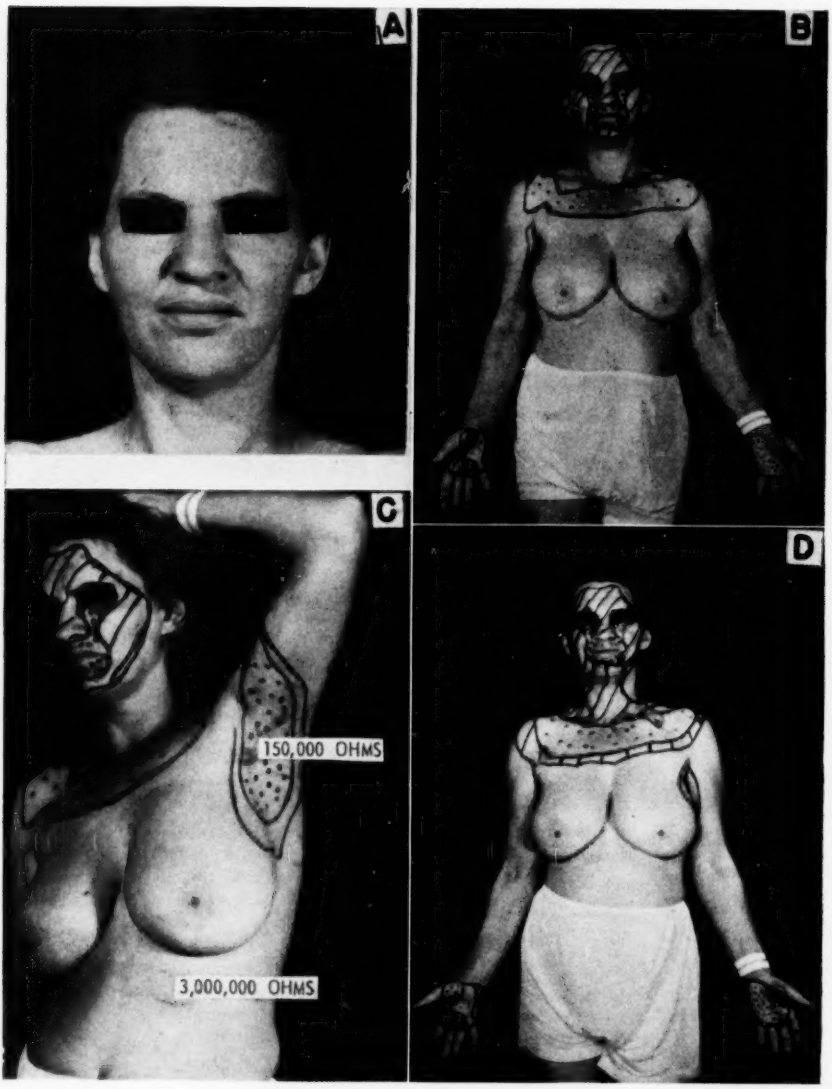

Fig. 1.—Mrs. M. B.: *B* and *C* show the skin resistance areas at room temperature. Striped and dotted areas are low resistance areas, indicating active sweat glands in these areas only. *D* shows pattern after heating for one hour.

warm weather. In her childhood she would soak her body with cold wet cloths and lie on marble floors in an effort to keep cool. During most of her life, she had been troubled during hot weather by polyuria, diarrhea, and a nasal discharge. Her only serious illness was persistent chronic bronchitis as a child. No relative on either side had ever been known to suffer from ectodermal dysplasia.

Examination of the patient revealed an obese, well-developed, middle-aged woman (Fig. 1*A*). The skin was very dry and thickened. There was a mucoid postnasal discharge. Slight sweating was noticed in the axillae only. The results of the remainder of the physical examination were essentially normal.

E. B., aged 10 years, was Mrs. M. B.'s daughter. She had been seen intermittently since the age of 3 years at the Johns Hopkins Hospital. Her first visit was for heat intolerance and chronic exhaustion. She was noted to have a saddle-shaped nose, and deformed teeth. These abnormalities were considered to be suggestive of congenital syphilis, but no evidence of this disease was

Fig. 2.—Patient E. B.: Low resistance areas are dotted. Patient has been heated in hot-air cabinet.

found. At the age of 7 years, she began to have a chronic cough, productive of mucopurulent sputum. She was found to have chronic bronchitis, nasopharyngitis, and ethmoiditis at various times.

Physical examination revealed an attractive 10-year-old girl. She had very dry skin, and many teeth, both upper and lower, were absent (Fig. 2*B*). There was absence of sweating, even when she was exposed to high environmental temperatures. The remainder of the physical examination showed an essentially normal condition.

SKIN RESISTANCE STUDIES

Both patients were examined periodically over three years. The studies were conducted in both summer and winter. To outline the areas of low and high resistance, the dermometer devised by Richter and Whelan was used. This instrument

and the technique for its use are described in detail elsewhere.[3] In brief, one electrode is clamped to the ear lobe of the patient. This is the indifferent electrode, and the resistance at this point is reduced nearly to zero by means of a skin puncture or application of electrode jelly under the electrode. The other electrode is a metal roller with which the entire body can be explored. No paste is used with the roller. The electrical resistance is determined with another instrument, the Whelan dermometer, which measures the amount of current that flows through the circuit while the voltage is kept constant.[4]

Skin resistance studies were made at approximately six-month intervals. The patients were studied in a cold room (55 F.), at room temperature, and after 60 minutes in a hot-air cabinet. In the cold room, no areas of low skin resistance were found. This finding is similar to that in most normal subjects, since at these low temperatures the sweat glands are normally completely inactive. At room temperature, the resistance remained extremely high in both patients over most of the body, but areas of lower resistance were detected over the face, the upper chest, the palms, the soles, and the axillae. After the patient had been heated for 30 minutes, the resistance still remained very high on all the skin, except on the aforementioned areas, where it became very low. Figure 1*B* and *C* shows the mapping record. Shading indicates low resistance and dotting very low resistance; all other areas showed a very high resistance. Figure 1*C* shows that, whereas the resistance was only 150,000 ohms on the axillae, it was 3,000,000 ohms on the trunk. Figure 2*A* and *B* shows the child's record, also made after 30 minutes in the heat cabinet. The areas of low resistance closely resemble those found on the mother's body.

CHEMICAL SWEAT TESTS

To obtain further evidence that sweat glands were absent in both patients, studies were made using the starch-iodine test of Minor.[5] In this test the subject's skin is painted at room temperature with the standard mixture of alcohol, castor oil, and iodine and dusted with rice-starch powder. Then the subject is heated. The areas where sweating occurs turn black. When the test was carried out for the two patients, only the palms, the soles, and the axillae turned black, indicating a number of functional sweat glands in these areas. On the face and neck, scattered black dots could be seen, indicating a few definitely functional sweat glands.

The results of the Minor test were confirmed by use of the method described by Silverman and Powell[6] for the testing of sweating function. In this method the part of the body to be tested is painted with an alcohol solution of ferric chloride and then placed for three minutes on paper impregnated with tannic acid. Where sweating occurs, ferric tartrate is dissolved out. This leaves a black precipitate on

3. Richter, C. P.: Instructions for Using the Cutaneous Resistance Recorder, or "Dermometer," on Peripheral Nerve Injuries, Sympathectomies, and Paravertebral Blocks, J. Neurosurg. **3**:181, 1946.

4. Whelan, F. G.: An Instrument for Use in Measuring Electrical Resistance of the Skin, Science **111**:496, 1950.

5. Minor, L.: Ueber erhöhten Hautwiderstand bei traumatischen Affektionen des Halssympathicus, Ztschr. ges. Neurol. u. Psychiat. **85**:482, 1923.

6. Silverman, J. J., and Powell, V. E.: Studies on Palmar Sweating: I. A Technique for the Study of Palmar Sweating, Am. J. M. Sc. **208**:297, 1944.

the paper. Various parts of the body were studied by this method, and the results were identical with those obtained with the Minor test.

GALVANIC SKIN RESPONSE

The Galvanic skin response is the term applied to the transient changes in skin resistance that are superimposed on the basic level of resistance.[7] This response can be initiated by psychic or physical stimuli or by electrical stimulation of the sympathetic paravertebral chain. In both these patients with ectodermal dysplasia, the galvanic skin responses, measured by the Wheatstone bridge method, were absent on the parts of the palms that contained no sweat glands; they were faintly present on the parts containing a few functional sweat glands. There was a direct correlation between the number of sweat glands and the magnitude of the Galvanic skin response, and in no areas was the response of magnitude comparable with that of the normal person.

ACTION OF PILOCARPINE

Intracutaneous injection of pilocarpine in a nonsweating area of the back resulted in excessive salivation, lacrimation, and increase in sweating in areas demarcated previously. This sweating was detected by the lowering of skin resistance. At the site of injection there was neither lowering of electrical skin resistance nor visible sweating.

VASOMOTOR ACTIVITY

When normal persons are exposed to cold temperature, a gradient of decreasing skin temperatures is seen between the trunk and the extremities. This difference depends on vasomotor activity. Both these patients without sweat glands demonstrated this decreasing skin temperature gradient when in the cold room.

RESULTS OF BIOPSY

Histological studies were made on specimens of the mother's skin. In a specimen 0.5 cm. square, taken from the back of the left forearm, no sweat glands could be seen in serial sections. The papillae were hypertrophied, and the corneum was thickened. In a specimen of the same size taken from the small of the back, one sweat gland was seen on examination of serial sections. This was a so-called apocrine type of sweat gland. In serial sections of the axilla, many apocrine type sweat glands were seen. Thus, there was histological confirmation of the fact that sweat glands were absent over large areas of the body.

COMMENT

Two patients with hereditary ectodermal dysplasia were studied with special emphasis on their sweating. Three different methods were employed—one electrical and two chemical. In addition, biopsies were made. The findings were all confirmatory, indicating an absence of sweat glands over most of the body. Sweating occurred only in those areas where normal persons show the greatest number of sweat glands and which are consequently the areas of lowest skin resistance, namely, the face, palms, soles, and axillae. However, both patients also gave evidence of

7. Féré, C.: Note sur des modifications de la résistance électrique sous l'influence des excitations sensorielles et des émotions, Compt. rend. Soc. biol. **5**:217, 1888.

slight sweat-gland activity over the anterior upper chest. This is the only difference between the low resistance areas demarcated after heating these patients and the areas of low skin resistance seen at room temperatures in normal subjects.[8] The significance of this chest area is unknown. It probably had been present in the mother since childhood, since the mother and daughter showed essentially identical patterns. Of interest is the fact that this chest area is often the first to be affected in patients with early scleroderma.

Study of these patients adds further evidence to support the concept that the electrical skin resistance is inversely related to sweat-gland activity, rather than to vasomotor activity or other changes accompanying sympathetic nervous system activity. The electrical resistance of the skin in the areas where sweat glands are congenitally absent is as high as that found in denervated or sympathectomized areas of the body in normal persons. In areas where sweat glands are present, the electrical resistance is dramatically lower and varies inversely with environmental temperature and consequent sweat-gland activity.

It was also found that the presence and magnitude of the galvanic skin response were directly related in these patients to the number of sweat glands present in the area under the electrodes.

SUMMARY

Results of studies on two persons, mother and daughter, both of whom displayed the classic symptoms of the rare anhidrotic type of hereditary ectodermal dysplasia, are presented.

Electrical skin resistance studies revealed areas of high arterial skin resistance over the entire body except the axillae, palms, and soles, where the electrical resistance was lower. In the face and over the upper chest the resistance was high, but relatively lower than over the remainder of the body surface.

Chemical testing of sweating by two methods and biopsy confirmed the absence of sweating in the areas demarcated by electrical skin-resistance studies.

Galvanic skin responses were absent from nonsweating palmar areas and were present, but very weak, in sweating palmar areas.

It is suggested that these findings add evidence to the idea that the electrical resistance of the skin is related to sweat-gland activity rather than to vasomotor changes.

Dr. C. P. Richter helped in and encouraged this study.

8. Richter, C. P.; Woodruff, B. G., and Eaton, B. C.: Hand and Foot Patterns of Low Electrical Skin Resistance: Their Anatomical and Neurological Significance, J. Neurophysiol. **6**:417, 1943.

TESTOSTERONE FOR APOCRINE DISEASES: HIDROSADENITIS, FOX-FORDYCE DISEASE

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THE REMISSION of apocrine gland diseases during pregnancy [1] challenges dermatologists to find the responsible factor and use it in nonpregnant patients with such sweat-gland disorders. The important role of hormones and endocrine glands in the gestational process strengthens belief that they also exert a predominant influence over the apocrine glands and diseases.

The literature on the endocrines in pregnancy is huge indeed, and excretion assays for individual products have been carried out by various investigators. Many articles and textbooks record the quantitative changes and relationships among the steroids during the progress of pregnancy. Venning has done much work in this field and accompanies one of her communications [2] with a composite curve of excretion of some of the steroids during pregnancy.

At first glance it seems logical to expect steroids augmented in pregnancy to aid the diseases of apocrine glands. But such hormones failed in these ills. This failure suggested the trial of endocrine products whose levels remain unchanged or even decrease with gestation. Venning's studies [3] on the excretion of 17-ketosteroids in pregnancy showed that there was little change in the total output when colorimetric procedures were used. She referred to the work of Dobriner,[4] who, in isolation studies, found that androsterone and etiocholanotone, the two major urinary 17-ketosteroids of normal women, are excreted in normal amounts during early pregnancy, but that by the eighth month androsterone has almost disappeared, while etiocholanotone is greatly reduced. Hain [5] reported that androgens decrease in the urine of pregnant women from 30 to 60 I. U. to 12 I. U. This result was independent of the sex of the fetus. In pregnancy there is a decrease of virilizing substances. Therefore, it is possible that this observed decrease in androgens really involves not only the pure male hormones but also a bisexual substance. According to Hain, all this has

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Testosterone propionate (perandren®) was supplied through the courtesy of Dr. Fred E. Houghton, Medical Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J.

1. Cornbleet, T.: Pregnancy and Apocrine Gland Diseases, A. M. A. Arch. Dermat. & Syph., to be published.

2. Venning, E. H.: Adrenal Function in Pregnancy, Endocrinology **39**:203, 1946.

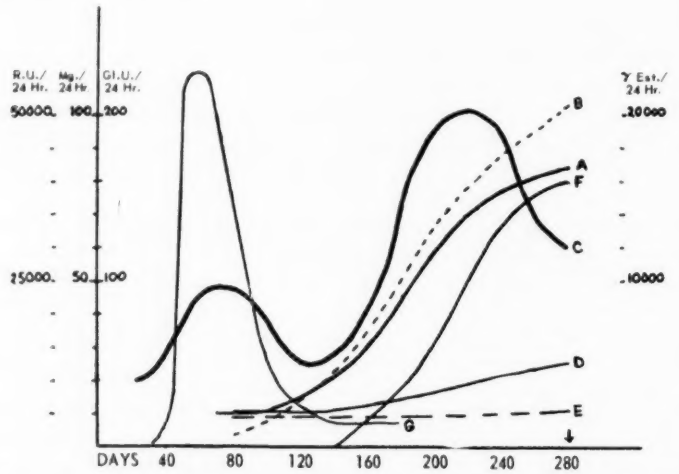
3. Venning [2]; personal communication to the author.

4. Dobriner, K., in Transactions of the Third Conference on Metabolic Aspects of Convalescence, New York, Josiah Macy, Jr., Foundation, March, 1943, p. 211; cited by Venning.[2]

5. Hain, A. M., cited by Courrier, R.: Endocrinologie de la gestation, Paris, Masson & Cie, 1945.

to be taken with caution, as it is not known how far the urine reflects the true endocrine activity.

The mammary glands are related developmentally to the apocrine glands. The former and their diseases are sensitive to the administration of testosterone. While metastases from mammary cancer in postmenopausal women respond equally to testosterone propionate and to estrogens, the superiority of testosterone in controlling the subjective symptoms, particularly pain, makes it appear to be the drug of choice.[6] Furthermore, metastases in skin and lymph nodes respond more frequently than do those in other soft tissues. Farber [7] treated chronic cystic mastitis with testosterone propionate. The mastitis is believed due to an imbalance between alpha-estradiol, the Graafian follicle hormone, and progesterone, the corpus luteum hormone. Testosterone may intervene to correct this relationship. Thirty-six of 48 women with mastitis improved with the use of testosterone. Testosterone is useful, too, for interrupting lactation.



Excretion rates of various hormones in pregnancy (average values in cases studied). *A* indicates pregnanediol; *B*, estrogens; *C*, corticoids measured in glycogenic units; *D*, ketosteroids (as determined by the dinitrobenzene method of Holtorff and Koch); *E*, ketosteroids (as determined by the antimony trichloride method of Pincus); *F*, theoretical excretion curve for pregnaneolones, assuming that the increase in difference between the two ketosteroid curves is due to these substances; *G*, gonadotropins, measured in rat units per 24 hours. Curve taken from a previous study on cases of normal pregnancy. (From Venning,[2] Figure 9; reproduced by permission.)

REPORT OF CASES

Ten patients with diseases of the apocrine glands have now been treated with testosterone, and several representative cases are reported here.

CASE 1.—*Hidrosadenitis suppurativa*

A Negro woman, 23 years old, had had lesions in the axillae for 18 months. Some had been treated surgically, and there were puckered scars. Other sites were active, discharging, and

6. Current Status of Hormone Therapy of Advanced Mammary Cancer, report of the Council on Pharmacy and Chemistry, J. A. M. A. **146**:471 (June 2) 1951.

7. Farber, E. P.: Use of Testosterone Propionate in Chronic Cystic Mastitis, West. J. Surg. **58**:693, 1950

tender. She received 25 mg. of testosterone propionate three times weekly, together with 300,000 units of penicillin in oil and wax intramuscularly. After a week tenderness subsided appreciably. After a month activity of lesions was reduced visibly, and six weeks later the lesions appeared healed. Without more treatment the patient remained well for the next two months.

CASE 2.—*Fox-Fordyce disease*

An 18-year-old Negro girl had lesions in the axillae, on the pubes, and a few on the breasts for three years. Testosterone propionate, in a dose of 25 mg., was administered subcutaneously three times weekly, with reduction of pruritus after 10 days and comfort in one month. The lesions "ironed out" in three months but were easily seen. The itching came back, and then the lesions recurred in three weeks without treatment. The height of past improvement was equaled within five weeks with renewed treatment. The patient was not followed further.

CASE 3.—*Hidrosadenitis*

A 32-year-old Negro woman had had lesions in the axillae, the perineum, and the upper inner surfaces of the thighs for three years. There were scarring, distortion of the surfaces, sinus formation with discharge of pus, and inflammatory tender foci. She received injections of 25 mg. of testosterone propionate three times a week without penicillin. Her condition showed considerable improvement after six weeks, although there were intervening periods of two or three days when relapses would occur. Apparently for complete involution over five months of continual therapy was required. Subjective relief, however, preceded objective corroboration.

CASE 4.—*Hidrosadenitis*

A white woman, 44 years old, had had deep abscesses and sinuses in both axillae for five years. There were marked edema and a profuse discharge. The patient complained of severe pain. The process had resisted all treatment, including roentgen therapy. Arrangements had been made for radical surgical treatment and plastic repair. Testosterone propionate was administered intramuscularly in 50-mg. doses twice a week. Improvement was slow, with the results that only after nine months of continual treatment did the sinuses close, the discharge cease, and the inflammation become quiescent. She responded much more slowly than did the younger women.

The remaining six patients, all women, included one with Fox-Fordyce disease and five with hidrosadenitis suppurativa. Three of the latter were given penicillin to augment the testosterone for the first two or three weeks. Testosterone propionate dosage was, for the most part, 25 mg. three times weekly, although in two patients 50 mg. was given twice weekly. The one patient with Fox-Fordyce disease in this group, like patient 2 above, after achieving gratifying improvement within four months, relapsed when treatment was halted. Not all the patients with hidrosadenitis went on to cure: Two dropped away, one after 14 weeks and the other after three months. Both of the latter, however, were considerably better at the end of observation.

COMMENT

The treatment of apocrine gland disease with testosterone requires a prolonged interval to achieve satisfactory results. Even then relapse may take place, especially in patients with Fox-Fordyce disease. Neither of our subjects with the latter condition was cured. At this time, it cannot be said whether testosterone therapy can do more than ameliorate Fox-Fordyce disease. The improvement with pregnancy is also only temporary. The outlook for cure in hidrosadenitis is more optimistic. The latter, though, is commoner than Fox-Fordyce disease, and its lesions are often scattered over the patient and do not lend themselves readily to minor and local plastic surgical procedures.

The entire group of patients reported on here included young and middle-aged women but no men, the same incidence as found by others. One patient, a Negro man, 20 years old, had a condition which was clinically and histologically acceptable as hidrosadenitis. He had urinary 17-ketosteroid output a little below normal, but there was no opportunity to treat him. For three of the women 17-ketosteroid urinary assays were made, with results all within normal ranges.

It is of present academic interest and future practical importance to know why apocrine diseases improve on treatment with testosterone. This form of therapy falls short of attaining a quick or complete cure. Nevertheless, the degree of improvement and, especially, the early subjective amelioration obtainable in such stubborn diseases are, indeed, gratifying. Almost all patients accept the therapy gladly as an alternative to extensive surgical intervention. The results obtained with testosterone tend to reemphasize the basic position of the endocrine glands and their hormones in the poorly understood pathogenesis of apocrine gland diseases. The older patients and those near menopause were more resistant to this form of therapy but responded, nevertheless, after much longer periods of treatment.

SUMMARY

Two women with Fox-Fordyce disease and eight with hidrosadenitis were improved or apparently cured by the use of testosterone propionate, with the addition, in several cases, of penicillin.

Previous observation of spontaneous improvement of apocrine gland diseases during pregnancy suggested the use of those hormones known to be in greater supply during gestation. None of these—estrogens, progesterone, pregnanediol, and gonadotropins—was of any benefit. The androgen level remains stationary or falls during pregnancy, but, despite the poor result to be expected on logical grounds, testosterone therapy relieved or cured apocrine diseases in 10 women. Older women toward the menopause responded much more slowly than did the younger ones.

A brief reference to and a discussion on the endocrine literature bearing on the pathogenesis of apocrine gland diseases are presented.

1819 W. Polk St. (12).

CONTACT X-RAY THERAPY OF THE COMMON WART

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AND
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TREATMENT of common warts is often one of the dermatologist's most perplexing problems. This is especially true if the warts are multiple or if they occur about or beneath the nails. Under these circumstances obtaining a cure may be more difficult than the successful management of, for example, the average basal-cell epithelioma.

Warts can be and are treated by a variety of agents. Evaluation of any treatment is difficult for various reasons for many verrucae seem to disappear spontaneously and, on occasion, in response to suggestion. It is also recognized that the virus can exist dormant in the skin for long periods of time,[1] and last, new lesions may appear at or near the site of treated lesions which are interpreted as recurrences.

During the past two and one-half years, 117 patients, presenting a total of 540 verrucae, were seen in a private office practice and received contact x-ray therapy. We have found it a convenient and efficient method. It is not our intention to offer the results of our group of patients as representing the percentage of cures which may be expected from this type of treatment, because, in order to try to determine the minimum effective dose, we have deliberately carried our dosage down to a level at which recurrences were common. Many of our patients, therefore, received amounts of radiation which we now know to be inadequate, and a higher rate of failure was thereby engendered.

EQUIPMENT AND TECHNIQUE

Our experience is based entirely on the use of a "Philips Metalix" contact therapy apparatus. It is operated at 47.5 kv. (constant potential) and a current of 2 μv. The inherent filtration is equivalent to 0.2 mm. Al., and the half-valve layer without added filtration is 0.3 mm. Al. The output is calibrated once each year by a certified radiation physicist. During the past three years the output at a target-skin distance of 18 mm. (actual "contact") has been 9,400 r, 9,000 r, and 9,600 r per minute, respectively, or from 150 to 160 r per second.

Andrews [2] has described the details of this apparatus, has pointed out its suitability for treating superficial lesions, and has quoted from Quimby,[3] Braestrup and

Read before the Section on Dermatology and Syphilology at the 100th Annual Session of the American Medical Association, Atlantic City, N. J., June 14, 1951.

1. Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948.

2. Andrews, G. C.: Contact Roentgen Therapy, Arch. Dermat. & Syph. **58**:118-127 (Aug.) 1948.

3. Glasser, O.; Quimby, E. H.; Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, New York, Paul B. Hoeber, Inc., 1944.

Blatz,[4] and others in discussing the physical factors involved. He has also called attention to certain mechanical deficiencies and has reemphasized the potential dangers to operating personnel unless precautions are taken.

The combination of low voltage and short target-skin distance results in the absorption of a large part of the radiation in the uppermost part of the skin, with a rapid dropping off of the depth-dose percentage deeper in the tissue. Braestrup [4] gives the depth-dose percentage with unfiltered radiation at a target-skin distance of 18 mm., 44 kv., and a field size of 2.45 cm. (diameter) as 23.0% at 1 cm., 6.7% at 2 cm., and 2.7% at 3 cm. In the case of verrucae it is possible to deliver an adequate dose to the pathologic tissue with a measure of safety to underlying structures not afforded by conventional x-ray technique.

These figures for depth-dose percentage are slightly lower than those which apply to the technique we have commonly used, in that our target-skin distance is 20 mm. instead of 18 mm. This working distance allows for the insertion, between the tube and the skin, of a sheet-lead shield 2 mm. thick with a suitable portal cut in the center. Actually, much thinner lead foil provides an adequate shield against radiation of this quality and can be as conveniently used, allowing the tube to be in direct contact for all practical purposes or at a target-skin distance of 18 mm.

The lesions are first pared with the scalpel, since it is essential to reduce each lesion to as flat a plane as is possible in order to insure an even distribution of radiation to the entire area. In subungual lesions the nails are carefully trimmed or clipped in order to expose the entire wart. Each lesion is then outlined with ink, a peripheral margin of 1 mm. of normal skin being allowed on all sides. Treatment of lesions on the hands is simplified in adults and cooperative children by having the patient hold the lesion, exposed through the portal, against the end of the tube which remains in a fixed position. The lead shield is supported by having the patient grasp one of its corners between the thumb and fingers of the opposite hand. The exposed digits are protected from stray radiation by a special cap on the tube or by covering the digits with lead foil. The treatment time averages only 15 to 20 seconds, and consequently a very short time is needed to treat a group of warts in this fashion. For lesions on the feet or elsewhere, and for some children with lesions on the hands, the part must be immobilized, the shield fixed in place, and the tube brought into position over the portal.

It is, of course, imperative that no area be exposed twice, and careful attention must be exercised to prevent such an accident when numerous lesions are to be treated. A list may be prepared before the treatment is started and each lesion checked as it is treated, or each treated area may be identified by an ink mark on the skin placed at the end of the exposure. Accurately kept charts, with diagrams of location and size of lesions and treatment fields, are, of course, mandatory.

Several lesions may be treated at one sitting. However, lesions in close proximity, for example those occurring periungually, are not treated at the same time. Treatment of lesions directly at the base of the nail sometimes causes dysplasia in the form of a depression of the nail as it grows out from that point. Defluvium of the nail occurred in one patient. Nail changes have occurred in only a few instances. They have all been temporary, and, except where the matrix had already been damaged by the wart as evidenced by nail changes prior to treatment, normal nails have resulted.

4. Braestrup, C. B., and Blatz, I. H.: Physical Factors of Low Voltage "Contact" Roentgen Therapy, Radiology **35**:198-205, 1940.

Patients are instructed to keep the treated parts clean with soap and water to prevent secondary infection. This complication was seen in only two patients of our group. Redness, inflammation, and tenderness of the site develop some 10 to 14 days after treatment, and apparent vesiculation sometimes occurs during the latter part of the second week and the third week. The reaction is intense but superficial and is subsiding at the end of three weeks when patients are regularly seen again. At that time the verruca is usually reduced to a keratotic mass, or it may have fallen off; if it has not fallen off, it can ordinarily be pared away easily with a scalpel, leaving intact epidermis beneath. The patient is then advised to apply a simple emollient until all the crusting and scaling disappears, usually a matter of one or two weeks. Ordinarily the site of treatment cannot be detected after 8 or 10 weeks.

ANALYSIS OF CASES

One hundred seventeen patients who had one or more warts were treated between September, 1948, and March, 1951. They ranged in age from 3 to 67 years. The distribution of patients according to ages is shown in the following tabulation:

Age Group, Yrs.	Patients, No.	Per Cent
Under 10	6	5
10 through 19	34	29
20 through 29	35	30
30 through 39	16	14
40 through 49	20	17
50 or over	6	5
Total	117	100

These patients presented a total of 540 lesions which were distributed regionally as shown in the tabulation below:

Location	Number of Lesions	Per Cent
Hands	358	66.3
Feet	153	28.3
Elsewhere	29	5.4
Total	540	100.0

The results of treatment were observed in 489 of the 540 treated lesions for a minimum period of three weeks. Evaluation of results is complicated by the use of supplemental therapy consisting of local application of dichloracetic acid in 155 lesions and bismuth subsalicylate, injected intramuscularly, in 18. A statistical comparison shows that the percentage of cures with this supplemental treatment was lower (76.3%) than with radiation alone (87.7%). This apparent paradox is probably accounted for by the fact that the more refractory lesions in which recurrences were most frequent received supplemental treatment. The over-all cure rate for all lesions treated was 83.6%.

Of 321 lesions on the hands, 276 (86.0%) were cured; of 141 lesions on the feet, 108 (76.6%) were cured; 25 of 27 lesions elsewhere on the body were cured, but the number of lesions is too small to be of statistical significance.

Treatment consisted of a single exposure varying, in the majority of our patients, between 2,100 and 2,500 r. A few large lesions were given doses as low as 1,500 r; a few very small lesions received up to 2,750 r. Andrews [2] recommended a dose of from 2,500 to 3,500 r. Our experience does not cover this range of

dosage, but it seems likely that a satisfactory cure rate could be expected with doses between 2,500 and 3,000 r, the size of the dose varying inversely with the size of the lesion.

SUMMARY AND CONCLUSIONS

A practical and effective method for the routine office treatment of common warts has been described. A rate of cure higher than the 83.6% obtained in our group of patients may be expected by the use of slightly higher doses than we have employed. We believe that this type of therapy has certain advantages over conventional x-ray techniques and over other forms of treatment. An appreciation of the necessity for extreme attention to detail in its use is essential to safety, both to the patient and to the operator.

25 Prospect Ave. (15).

ABSTRACT OF DISCUSSION

Dr. John E. Rauschkolb, Cleveland: There are just a few things I want to say in closing. The advantages, in our opinion, of the physical factors involved are, first, low kilovoltage and short skin-target distance, allowing the absorption of the greater part of the radiation in pathologic tissue with relative safety to other parts of the cutaneous structures, resulting in rapid healing with no evidence of deleterious effect. Second, there is an advantage in rapid administration which makes more convenient treatment of multiple lesions, especially in children. Third, there are advantages in common with any type of x-ray technique, namely, that no anesthesia is required and better cosmetic results are usually obtained.

There are the following limitations in this treatment: First, the tremendous output requires extreme attention and accuracy of the operator to avoid serious mistakes. Second, small variations in measurement of target-skin distance mean large variations in dose. Lesions with irregular surface may receive nonuniform doses of distribution.

Dr. F. J. Eichenlaub, Washington, D. C.: Since the early 1920s, when the late Dr. Hazen and I reported on the treatment of plantar warts with x-rays, I have been interested in radiation treatment of warts. I am interested in the use, and especially in the abuse, of this therapeutic modality.

The proper use of x-ray in the treatment of warts has consisted in the application of a reasonably efficient dose sharply limited to each wart to be treated. In our hands this has meant the administration of not more than 1,200 r to each lesion, unfiltered, and not involving an area of more than 5-mm. surface for any one lesion. Each wart is so treated individually and the dose repeated once in three or four weeks, if necessary. If this is not effective, measures other than x-ray are employed.

The abuse, mostly, I am glad to say, not by dermatologists, consisted of using heavily filtered x-rays, often with 2 or 3 mm. Al., or even with brass filtration, and treating areas from 1 to 4 cm. or more in diameter including several warts in the area. This has resulted in many chronic x-ray ulcerations, requiring plastic surgery for cure.

Dr. Rauschkolb is now presenting the results of contact x-ray therapy in the treatment of warts, which offers a new element of safety.

If I understand his figures correctly, about 75% of the x-ray radiation is absorbed in the first 1-cm. thickness of tissue. Since most warts, even after paring, are at least 5 mm. deep, it would appear that the wart itself would absorb at least 50% of the radiation administered. If some 60 to 70% of warts can thus be cured, it would seem that contact radiation should be a relatively safe and satisfactory treatment.

Nevertheless, a word of caution should not be amiss. A dose of 2,500 to 3,000 r is still a considerable amount of x-ray. While there will probably be little damage of the deeper portions of the corium and dermis, this amount of x-ray can still produce radiation effects in the epidermis itself, and it is there that radiation epithelioma occurs.

It is to be hoped, therefore, that those who follow the treatment advocated by Dr. Rauschkolb, will also observe all the safety precautions he has advocated in his very able presentation.

BULLOUS VARIETY OF INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER)

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AND
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MONROE, MICH.

INCONTINENTIA pigmenti is a rare congenital anomaly. It was first fully described under this name by Sulzberger [1] in 1927, and by Siemens [2] in 1929 as "melanosis corii degenerativa." Sulzberger's case had been previously presented by Bloch [3] in 1925, and Siemens' case was discussed first in a dissertation by Lechleuthner.[4] According to Becker,[5] the condition was evidently described first by Bardach [6] as a systematized nevus. Carney [7] recently reviewed 32 cases from the literature (including the one reported in this paper) and added 5 more of his own. Additional cases are reported by Heilesen [8] (two cases), Jaramillo and his associates,[9] Doornink [10] (three cases), and Uebel and his co-workers [11]; the last authors cited two additional observations (Hora, Gerard). This would bring the total to about 46 cases of incontinentia pigmenti. Actually the number of cases presented is

From the Departments of Dermatology and Pediatrics, Marshfield Clinic and St. Joseph's Hospital (Dr. Epstein and Dr. Vedder), and the Department of Dermatology, Wayne University Medical College (Dr. Pinkus).

1. Sulzberger, M. B.: Über eine bisher nicht beschriebene congenitale Pigmentanomalie (Incontinentia pigmenti), Arch. Dermat. u. Syph. **154**:19-32, 1927.

2. Siemens, H. W.: Die Melanosis corii degenerativa, eine neue Pigmentdermatose, Arch. Dermat. u. Syph. **157**:382-391, 1929.

3. Bloch, B.: Eigentümliche bisher nicht beschriebene Pigmentaffektion (Incontinentia pigmenti), Schweiz. med. Wchnschr. **56**:404, 1926.

4. Lechleuthner, cited by Doornink, F. J.: Dermatologica **102**:63-72, 1951.

5. Becker, S. W.: Personal communication to the authors.

6. Bardach, M.: Systematisierte Naevusbildungen bei einem eineiigen Zwillingspaar: Ein Beitrag zur Naevusätiologie, Ztschr. Kinderh. **39**:542-550, 1925.

7. Carney, R. G.: Incontinentia Pigmenti: A Report of 5 Cases and Review of the Literature, A. M. A. Arch. Dermat. & Syph. **64**:126-135 (Aug.) 1951.

8. Heilesen, B.: Incontinentia pigmenti, Acta dermat.-venereol **28**:544-551, 1948.

9. Jaramillo, R.; Manterola A., and Rosselot, J.: Incontinentia pigmenti, Rev. chilena pediat. **19**:654,662, 1948; abstracted, Excerpta Med. XIII **3**:1832, 1949.

10. Doornink, F. J. Über Incontinentia pigmenti und über die Siemens-Bloch'sche Pigmentdermatose, Dermatologica **102**:63-72, 1951.

11. Uebel, H.; Ludwig, A., and Korting, G.: Zur Kenntnis der Incontinentia pigmenti (Bloch-Sulzberger), Arch. Dermat. u. Syph. **190**:114-124, 1950.

greater, because similar instances have been published under other titles, such as dermatitis herpetiformis (Wilson,[12] Rothwell,[13]) and probably also as systematized nevi. Our case is presented because of its unusual features and because we have been able to study the various phases histologically.

REPORT OF A CASE[14]

The patient, B. J. V., a girl, was first seen on Oct. 22, 1947, at the age of 13 days. At the time of birth the attending physician had noted a papular eruption of the buttocks and thighs. Two days later periodic twitching of the left arm and leg was observed, which lasted for about one week. The next day a patchy eruption appeared on the body, arms, and legs. The family history was noncontributory.

When first seen at the clinic the child presented a generalized bullous eruption which was most pronounced on the legs and arms but also present on the trunk and face. There were grouped and linearly arranged vesicles and bullae, similar to those in Figure 2*A* of Carney's[7] Case 2. There were also red areas of infiltration and oddly configurated brownish-black pigmentations at the sites of previous lesions.

The Nikolski sign was negative. Cultures from early blisters were negative. There was a mild anemia, a leucocytosis of between 8,000 and 20,000, and an eosinophilia from 18 to 50% in the blister fluid.

Clinically a diagnosis of a bullous eruption, most likely dermatitis herpetiformis, was made.

A thorough general examination at that time revealed no obvious abnormality except that the child was very small, measuring 19½ in. (49.5 cm.) in length. Circumference of the head was 33 cm., of the chest, 31 cm.

At the age of 4 months the blisters gradually disappeared and reappeared only in small numbers from time to time. Since then bizarre pigmentation and red infiltrated papules, as well as firm elevated plaques, some hyperkeratotic and linear, have dominated the scene. At the age of 16 months the clinical picture was characterized by the typical pigmentations (Fig. 1) all over the body, arms, and legs, and even on the face and scalp. On the scalp were two spots of atrophic alopecia. There were no signs of follicular atrophoderma. The nails were normal. Roentgenologic examination (Dr. J. M. Wickham), at 16 months, of head and extremities revealed no abnormalities, except that the bone age corresponded to that of a 12-month-old girl. Roentgenologic examinations of the teeth at 3 years showed the absence of temporary and permanent teeth in the lower central region. The developing upper central permanent teeth showed a very irregular cutting edge.

On Feb. 28, 1949, at 28 months, the child suffered the first of a series of convulsive seizures which lasted for several hours. Similar episodes occurred later and were followed by a hemiparesis of the left side. On Dec. 22, 1950, convulsions of the left side started, which lasted for seven hours. The mother noticed that the child had been restless for about a week preceding the convulsions. As always during this prodromal time, the marks on the head and body became swollen, red, and itchy. The child was also nauseated. Following the convulsions, the left side of the face and the left extremities were partially paralyzed, and speech was impaired. Dr. T. C.

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12. Wilson, D. J.: Dermatitis Herpetiformis in an Infant: Report of Case, Arch. Dermat. & Syph. **44**:58-62 (July) 1941.

13. Rothwell: Dermatitis Herpetiformis? Pemphigus? Arch. Dermat. & Syph. **9**:646 (May) 1924.

14. The child was presented Sept. 18, 1948, at the meeting of the Minnesota Dermatological Society as "A Case for Diagnosis (Dermatitis Herpetiformis?)." During the discussion Dr. Carl Laymon and Dr. H. E. Michelson suggested the diagnosis of incontinentia pigmenti. The case was also mentioned by Dr. H. Pinkus at the 10th annual meeting of the Society for Investigative Dermatology, June 12, 1949, during the discussion of Dr. Helen Curth's paper (J. Invest. Dermat. **13**:233, 1948).

Erickson of the neurosurgical department of Wisconsin General Hospital found a spastic hemiparesis on the left. A pneumoencephalogram revealed a general shift of midline structures toward the right; the right lateral ventricle was considerably and generally dilated; the third ventricle was increased in size. A diagnosis was made of extensive right-sided cerebral atrophy with general decrease in size of this hemisphere.

The child was seen last on May 8, 1951. The hemiparesis of the left side had improved. The girl is in good health; she walks and is very active. The pigmentation is fading in those areas which were exposed to sunlight.

Fig. 1.—Characteristic picture of incontinentia pigmenti, pigmentary stage; age 16 months.

Histopathology.—Five biopsies done when the infant was 19 days, one month, 7, 12, and 16 months old, respectively, permitted us to analyze the pathologic process. The histologic changes may be summarized as follows:

In the first two specimens, there was diffuse infiltration of the epidermis with eosinophilic leucocytes which also filled large intraepidermal vesicles (Fig. 2*A*). The first one also showed similarly heavy eosinophilic infiltrate in the corium, particularly around blood vessels. Cutaneous eosinophilia was reduced in the second specimen which instead showed much granular debris around the veins. Eosinophiles were practically absent in the epidermis as well as in the corium in

all later specimens. Apparently independent of eosinophilia, there was a most peculiar disturbance of keratinization in the epidermis. Single dyskeratotic cells and whorls of prickle cells, often with central keratinization, were already present in the first specimen (Fig. 2*B*) and increased greatly in number up to 12 months of age when they often formed ascending strings and almost honeycombed the rete (Fig. 3*A*). The last specimen showed little of this phenomenon. The epidermis in general had at least twice normal thickness in all specimens and always was hyperkeratotic. In the third biopsy at 7 months, however, there was truly verrucous and papillomatous hypertrophy (Fig. 4*A*), which had again largely subsided at 1 year.

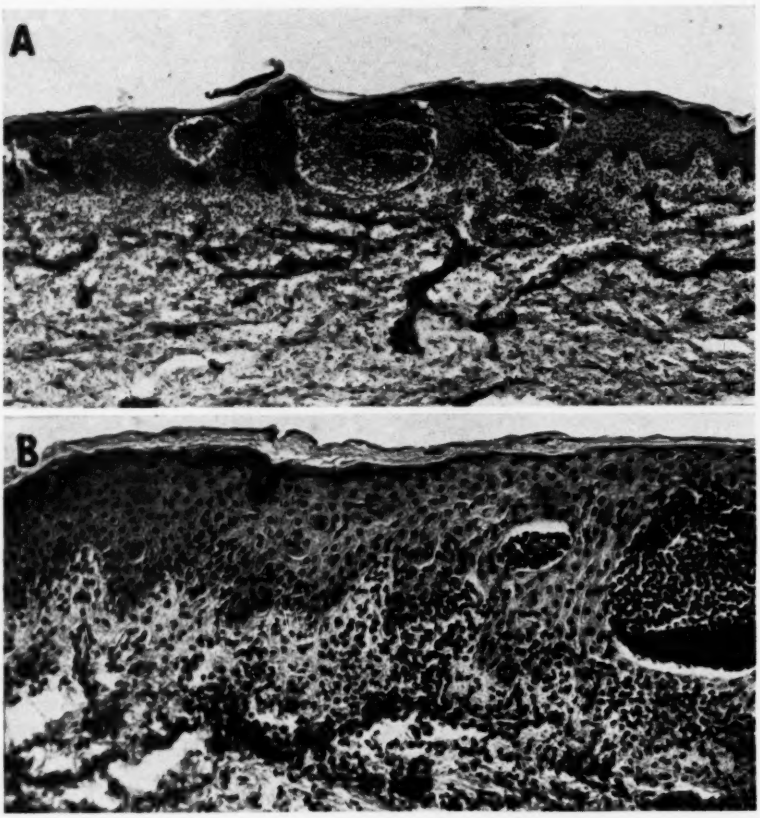

Fig. 2.—Bullous stage of incontinentia pigmenti at the age of 19 days. *A*, acanthosis, parakeratosis, and large intraepidermal vesicles filled with eosinophilic leucocytes; diffuse and perivascular leucocytic infiltrate in the upper corium and invading the epidermis. *B*, details of the epidermis; whorl arrangement of prickle cells in the portions less affected by eosinophilic infiltrate. Structures resembling sweat-duct openings in the left half of the figure were shown by serial sections to be just centers of keratinization. No sweat ducts were present under this part of the epidermis.

Melanin was at first present, in somewhat reduced amount, in the basal cells of the altered epidermis and was also present in junctional dendritic cells. The amount of pigment gradually decreased in the epidermis, while increasingly numerous histiocytic melanophores appeared in the papillae and subpapillary layer (Fig. 4*B*). The basal cells became vacuolated and were uneven in size and arrangement. The last and entirely consistent disturbance of the epithelial structures

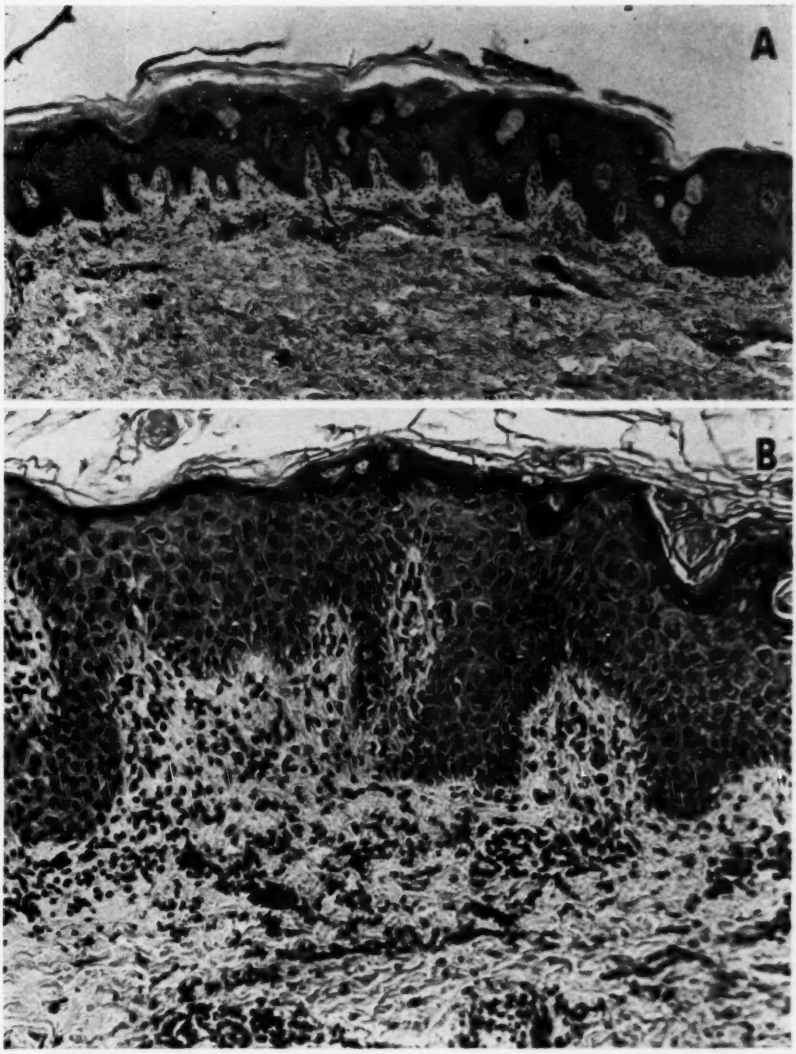

Fig. 3.—Persistent disturbance of keratinization and incontinentia pigmenti at age of 1 year. *A*, acanthosis, hyperkeratosis, and intraepidermal centers of cornification which often simulate sweat ducts; mild perivascular infiltrate and melanophores in the upper corium. *B*, high-power view of a section similar to *A*, showing irregularity of the basal layer and some invasion of the epidermis by inflammatory cells; dyskeratotic cells and whorls in the epidermis; heavy pigment deposits in the subpapillary layer.

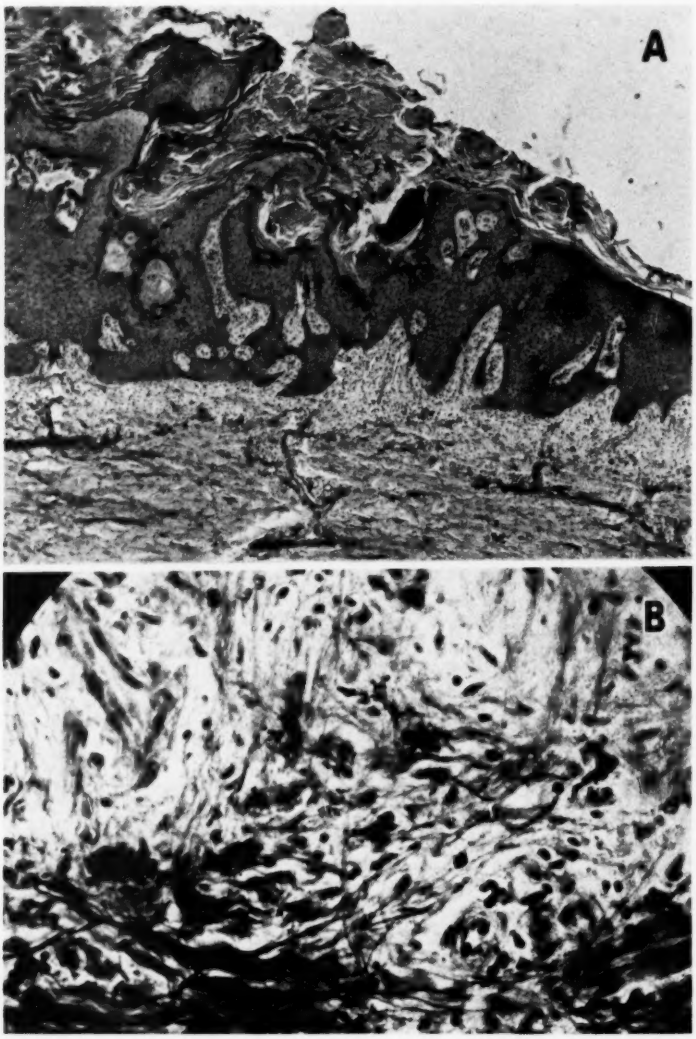

Fig. 4.—Hypertrophic stage at age of 7 months. *A*, extreme acanthosis, papillomatosis, and verrucous hyperkeratosis with intraepidermal centers of cornification; reduction of inflammatory infiltrate and early fibrosis in the upper corium. *B*, detail of subpapillary layer; clumped melanin in histiocytes; edema and reduction of elastic fibers in the upper part of figure; endothelial swelling and increase of fixed tissue cells; orcein and Giemsa.

was a complete absence of hair follicles and sweat glands in the abnormal parts of the skin of all specimens, while they were well developed in the normal parts.

Cutaneous changes consisted of the aforementioned eosinophilic infiltration in the early stages which later gave room to some edema, reduction of elastic fibers, and fibrosis in the corium. While arteries remained normal, the veins in the second to fourth biopsies appeared increasingly surrounded, first by granular debris, then by broad sheaths of fibroblasts and histiocytes, the latter often containing melanin. This change had subsided somewhat in the last specimen.

COMMENT ON HISTOLOGIC FINDINGS

The first biopsy seemed to confirm the clinical diagnosis of congenital dermatitis herpetiformis. However, in the light of following events, we believe that this represents only an acute, possibly reactive phase in the process which appears to be basically a severe disturbance of the ectodermal component of the skin. This disturbance manifests itself in three ways: disturbance of pigmentation, disturbance of keratinization, and agenesis of skin appendages. All three of these are not universal

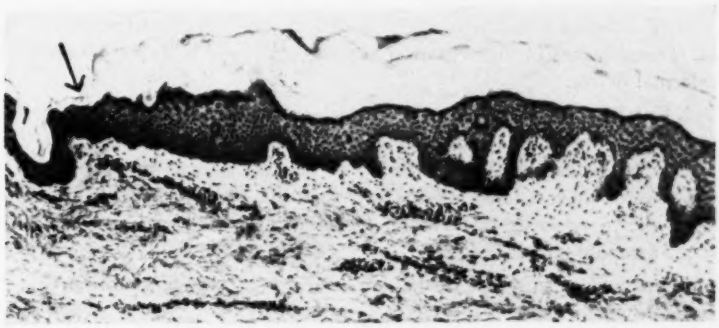

Fig. 5.—Fully developed incontinentia pigmenti at age of 16 months; hyperkeratosis, acanthosis, and a few intraepidermal whorls; poorly developed basal layer without pigment; mild perivascular infiltrate. Much of the dark material in the corium is pigment in melanophores. Arrow indicates the abrupt change from normal to abnormal epidermis.

but localized together in sharply circumscribed areas of the skin, thus fulfilling the criteria of a nevoid disturbance. The pigmentary disturbance seems to be similar to previously reported cases of incontinentia pigmenti. The absence of appendages in our case is thought to be due to agenesis rather than atrophy, because prenatal inflammation severe enough to destroy already-developed glands would surely have left some scarring. The general structure of the corium, however, is completely normal. The disturbance of keratinization is most unusual. The whorls and centers of keratinization are probably analogous to the horny cysts of verrucae seniles (seborrheic keratoses) and of certain epidermal nevi. They are an additional argument in favor of the nevoid character of the disturbance, although similar whorls are occasionally found in pemphigus and epidermolysis bullosa.

CLINICAL APPEARANCE

Our case corresponds in many respects to those described as incontinentia pigmenti. Our patient was abnormally small, showed faulty dentition, and is in this

respect similar to Sulzberger's [15] second case. Pseudopelade-like lesions were mentioned in Sulzberger's cases, and stressed by H. O. Curth.[16] Recurrent convulsions with hemiplegia, however, as seen in our patient, have not been described in the literature. Spastic tetraplegia (Little's disease) in incontinentia pigmenti was reported by Siemens [2] and Carney.[7] There are several factors that indicate that the neurologic symptoms in our case are related to the congenital abnormality. The convulsions and hemiplegia were preceded by itching and inflammation of the skin markings and were always restricted to the left side, the same side which presented the linear hyperkeratotic lesions. There were also malformations of other ectodermal derivatives present (teeth, epidermis, and adnexa of skin).

The linear arrangement in combination with somewhat *coup-de-sabre*-like scalp lesions and with central nervous symptoms brings to mind linear scleroderma. The association of this condition with abnormalities of the spine and nervous system has been discussed recently by Rubin.[17]

The combination of defects of teeth, hairs, and cutaneous glands is also found in cases of so-called "ectodermal defect." Our case differs from that group in the fact that the malformation is not generalized or diffuse, but is localized in sharply limited patches. Disturbances of pigmentation are not associated with the generalized type of ectodermal defect.

H. O. Curth [16] has collected cases in which incontinentia pigmenti was combined with dwarfism, osseous malformation, and a peculiar type of cutaneous atrophy (follicular atrophoderma). Our patient is of unusually small stature, but so far no localized osseous defects have become apparent. The lack of cutaneous adnexa we believe is due to agenesis rather than secondary atrophy, and the skin does not exhibit the atrophic follicular pattern described by H. O. Curth.

One more feature of our case should be mentioned, the high eosinophilia in the early stages of the disease. During the first two months of life, the eosinophilia of the blood ranged between 18 and 50%. The blister fluid contained 90% to 94% eosinophiles, and the infiltrate of the early sections was made up nearly exclusively of eosinophiles. After the bullous eruption had subsided more or less, after the sixth month of life, the eosinophiles in the blood were within the normal range; at that time eosinophiles were also completely absent in the infiltrate.

COMMENT

It would seem to us that incontinentia pigmenti is the skin part, or, as Wiener [18] calls it, the "dermadrome" of a syndrome that affects various structures of ectodermal and, possibly, of mesodermal origin (brain, eyes, teeth, epidermis, hair, skin glands, and melanoblasts). The abnormal pigmentation which characterizes the condition is only one, and really the latest, of the cutaneous manifestations of the disease.

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15. Sulzberger, M. B.: Incontinentia Pigmenti (Bloch-Sulzberger), Arch. Dermat. & Syph. **38**:57-69 (July) 1938.

16. Curth, H. O.: Follicular Atrophoderma and Pseudopelade Associated with Chondrodystrophia Calcificans Congenita, J. Invest. Dermat. **13**:233-248, 1949.

17. Rubin, L.: Linear Scleroderma: Association with Abnormalities of the Spine and Nervous System, Arch. Dermat. & Syph. **58**:1-18 (July) 1948.

18. Wiener, K.: Skin Manifestations of Internal Disorders (Dermadromes), St. Louis, C. V. Mosby Company, 1947.

Inflammatory State of Incontinentia Pigmenti.—A check of the literature reveals that in many instances inflammatory changes, at times also vesicles and bullae, preceded the pigmentation. Carney [7] tabulated occurrence of these changes and also the presence of hyperkeratotic or "warty" lesions. When these observations are correlated, there appears a sequence of events which is more or less apparent in different instances. Heilesen,[8] as far as we can see, was the first to divide the disorder into different stages. It seems to us that there are three definitive though overlapping stages:

1. Bullous or vesicular stage, noticed immediately after birth.
2. Hypertrophic stage, characterized by infiltrative and hyperkeratotic papillomatous lesions.
3. Pigmentary stage, showing the "bizarre irregularly formed spots of a peculiar slate brown."

The frankly bullous variety of incontinentia pigmenti seems to be rather rare. There is some reason to believe that some of these bullous cases have not been recognized as variants of incontinentia pigmenti. Haxthausen [19] originally diagnosed Heilesen's [8] case as lichenoid, partly bullous dermatitis. Wilson,[12] in 1941, reported a case similar to ours as dermatitis herpetiformis in an infant. Dr. Wilson [20] reexamined the child in 1948 and found definite pigmentations, confined to the right inguinal regions, which conformed in configuration to incontinentia pigmenti.

There are two more cases described as dermatitis herpetiformis of the newborn by Willi and Burckhardt,[21] and one by Rothwell,[13] which also may represent the bullous variety of incontinentia pigmenti.

Etiologic Considerations.—Sulzberger [1] proposed a hypothesis of a congenital pigmentary anomaly due to a pathologic permeability of the melanoblasts. Becker [5] considers the increased pigmentation a postinflammatory melanosis. This position appears plausible when one considers the inflammatory conditions which often have preceded the pigmented phase.

It might be mentioned that long-lasting cutaneous pigmentation which is similar to that of incontinentia pigmenti from a purely morphogenetic point of view is often found in lichen planus. In that disease, the basal cells degenerate and discharge their pigment into the corium, where it is deposited in histiocytic melanophores and may remain as a "tattoo" for many months after the inflammatory eruption has subsided. The pigmentation of lichen planus may be considered an instance of symptomatic incontinentia pigmenti in an inflammatory dermatosis. Doornink [10] shares a similar opinion. He found incontinentia pigmenti, a pigmentary insufficiency of the basal layer, also in Riehl's melanosis, in lupus erythematosus, parapsoriasis, lichen planus, poikiloderma, and other dermatoses. Becker [5] believes that incontinentia pigmenti is a "systematized nevus not in the sense of containing nevus cells, associated with many other abnormalities." Caro,[22] who examined the sections of our case, concluded that the lesion was an epidermal nevoid disturbance.

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19. Haxthausen, H., cited by Heilesen.[8]

20. Wilson, D. J.: Personal communication to the authors.

21. Willi, H., and Burckhardt, W.: Ein Fall von Dermatitis herpetiformis Dühring beim Neugeborenen, Kinderärztl. Praxis **12**:144-148, 1941.

22. Caro, M. R.: Personal communication to the authors.

In agreement with these opinions we believe that one can push the pathogenesis back another step. Not only is the clinical pigmentation secondary to inflammation, but the inflammation is secondary and a reaction to an epidermal abnormality which must have originated during fetal life, if it is not genetically fixed. We might attempt to localize in time the beginning of the disturbance. The spotty distribution of the pigmentary disturbance suggests that it originated after the melanoblasts reached their final position in the skin. This, according to Zimmermann and Cornbleet,[23] is accomplished at 3½ months of fetal life. Development of teeth and hair germs in the fourth to sixth embryonic months would seem to put the disturbance into the second trimester.

Uebel and his co-workers [11] suggested the possibility that a presumable virus infection of mother and fetus which occurred during the sixth month of pregnancy may have been of etiologic significance in their case. The only other case in which an intercurrent infection during pregnancy has been reported is Haber's. More evidence must be awaited before one can draw any such conclusions. Search for obviously minor virus infections, such as herpes simplex, and virus studies on mother and child may add evidence to Uebel's theory.

Uebel and his associates also called attention to certain vascular and inflammatory changes affecting especially the deeper arteries in the form of perivascular foci of inflammation, degenerative changes, etc. These changes suggested to these authors a relationship between incontinentia pigmenti and allergic-hyperergic inflammation. The possibility of some allergic mechanism has also occurred to us, especially because of the episodes of pruritic flare-ups and swelling of the erythematous lesions and because of the eosinophilia. It is also known that convulsions may be due to allergic cerebral processes.

We would like to add a remark about nomenclature. The term incontinentia pigmenti has been considered inadequate by several authors (Goldsmith,[24] Becker,[5] Doornink),[10] mainly because the pigmentary aberration is only one element of the disorder, and perhaps a minor one. The same objection is valid in regard to Siemens' [2] term of "melanosis corii degenerativa" or Doornink's suggestion of labeling it a pigment dermatosis ("Siemens-Bloch's Pigmentdermatose"). It seems to us that regardless of its admitted inadequacies, the designation "incontinentia pigmenti (Bloch-Sulzberger)" has been generally accepted for the syndrome, and it would only lead to confusion to change it now.

SUMMARY

An unusual case of incontinentia pigmenti is presented. It originated as a bullous dermatitis and was accompanied by other defects, such as extensive cerebral atrophy associated with convulsions and hemiplegia, deformity of teeth, and agenesis of skin appendages in the involved areas.

Incontinentia pigmenti is only one of the cutaneous manifestations of a congenital disorder which affects various structures of ectodermal and possibly mesodermal origin.

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23. Zimmermann, A. A., and Cornbleet, T.: Development of Epidermal Pigmentation in the Negro Fetus, J. Invest. Dermat. **11**:383-395, 1948.

24. Goldsmith, W. N., in discussion on Haber, H.: Incontinentia Pigmenti (Bloch-Sulzberger), Brit. J. Dermat. **61**:104-105, 1949.

A study of the literature, as well as the clinical and histopathologic observations in our case, suggests that incontinentia pigmenti in its fully developed form presents three overlapping stages of its skin manifestations:

(*a*) Bullous or vesicular stage

(*b*) Hypertrophic stage

(*c*) Pigmentary stage

The cause of incontinentia pigmenti is discussed.

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INVESTIGATIONS OF SOME SIDE-EFFECTS OBSERVED IN SYPHILITIC PATIENTS TREATED WITH PENICILLIN

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MANY REPORTS [1] on the reactions to and side-effects of penicillin have been published, and in most cases these responses have been attributed to a specific sensitization to crystalline penicillin. However, there are a few authors who have described reactions which were thought to be caused by a different mechanism.

Blaich,[2] in experiments with mice, found marked hyperemia in the ovaries and the vaginal mucosa and also observed an increase in the secretory function of the pancreas after injections of penicillin. In humans he observed a mild gastric hypersecretion in 50% of patients, following a single injection of penicillin. In a series of 29 women, he described hyperemia and haziness in the outline of capillaries investigated by means of capillary microscopy, both increasing with repeated doses of penicillin. He also noted a corresponding increase in capillary permeability in these patients. He attributed these findings to cholinergic stimulation.

Goetz and his collaborators [3] demonstrated that small doses of penicillin increased the erythematous response of the human skin to ultraviolet rays, increased the whealing effect of atropine, and also increased the muscular response to electric stimulation.

From the Subdepartment of Dermatology, Department of Medicine, Royal Victoria Hospital, and the Department of Pathology, McGill University.

1. (*a*) Brown, E. A.: Reactions to Penicillin: A Review of the Literature, 1943 to 1948, Ann. Allergy **6**:723, 1948. (*b*) Peck, S. M.; Siegal, S.; Glick, A. W., and Kurtin, A.: Clinical Problems of Penicillin Sensitivity, J. A. M. A. **138**:631 (Oct. 30) 1948; Immunologic Relationships of the Antibiotics and Trichophytin, J. Invest. Dermat. **9**:165, 1947.

2. (*a*) Blaich, W.: Untersuchungen über den Wirkungsmechanismus des Penicillins: Wirkung von Penicillin auf den Oestrus geschlechtsreifer weisser Mause, Arch. Dermat. u. Syph. **188**:340, 1949; (*b*) Untersuchungen über den Wirkungsmechanismus des Penicillins: Wirkung von Penicillin auf die Ovarien infantiler Mäuse, ibid. **188**:348, 1949; (*c*) Über den Einfluss von Penicillin auf den Arbeitsrythmus des Mäusepankreas, Arch. exper. Path. u. Pharmakol. **207**:70, 1949. (*d*) Blaich, W., and Ehring, F.: Untersuchungen über den Wirkungsmechanismus des Penicillins: Beobachtungen an den Hautkapillaren während der Penicillinbehandlung, Arch. Dermat. u. Syph. **188**:676, 1949. (*e*) Blaich, W., and Tushaus, B.: Der Einfluss des Penicillins auf die Magenfunktion, Fortschr. Diagnostik u. Therap. **1**:2, 1949; (*f*) Kolloidosmotische Bestimmungen als Mass für den capillarerweiternden Effekt des Penicillin, Arch. Dermat. u. Syph. **188**:683, 1949.

3. Goetz, H.; Kehrer, K., and Muller, H.: Über Penicillinnebenwirkungen, Arch. Dermat. u. Syph. **190**:125, 1950.

We have had an opportunity to observe several side-effects from penicillin which have not been reported and which did not appear to be due to specific sensitization.

MATERIALS AND METHODS

One hundred patients, 48 males and 52 females, who registered consecutively, without selection, at the syphilis clinic of the Royal Victoria Hospital were studied. All were syphilitics, varying in age from 12 to 76, for whom a diagnosis of latent late syphilis was made in the majority of cases.

A careful history was taken in each case with special regard to (1) previous penicillin therapy, (2) cutaneous or respiratory allergy, (3) fungous infection, (4) seborrhoea and seborrheic disorders, and (5) hyperhidrosis (as evidence of cholinergic stimulation).

Fig. 1.—Grade I abnormal response, 10 minutes after stroking.

All patients were carefully examined with regard to skin disorders (symptoms of allergy, mycotic infection, seborrhoea, and hyperhidrosis). Penicillin procaine in oil [4] with aluminum monostearate, 5 to 7 injections, was administered to all patients, with the exception of seven who received procaine penicillin in aqueous suspension. Intracutaneous tests with penicillin, trichophytin, and procaine were performed for 75 patients.

Each patient was stroked on the back and buttocks with a wooden tongue depressor prior to institution of therapy, twice weekly during treatment, once weekly after termination of therapy for two months, then once a month for a year, and the intensity of the vascular response was listed. All patients were carefully examined and questioned with regard to any treatment reactions, skin manifestations or anything attributable to penicillin therapy during the follow-up period of 12 months.

4. Penicillin used in these investigations was donated by the following pharmaceutical houses: Ayerst, McKenna and Harrison, Ltd.; Bristol Laboratories, Inc., and E. R. Squibb & Sons.

Fig. 2.—Grade II abnormal response, 20 minutes after stroking.

Fig. 3.—Grade III abnormal response, 10 minutes after stroking. Erythema had faded, showing additional pilomotor reflex and persistent follicular swellings outside stroked areas.

A complete hemogram [5] was performed for 21 patients, before, during, and after therapy, and for an additional 25, a differential count was done before and after therapy.

Ninety patients were followed for a period of one year or more, 4 for nine months, 3 for three months and 3 for one month. In the last group, one died. The other two were subsequently located after 18 months and at this time displayed a Grade II abnormal response to stroking.

The intensity of response to stroking was listed as follows:

(*a*) Normal, no response or a faint line of erythema disappearing in two to three minutes.

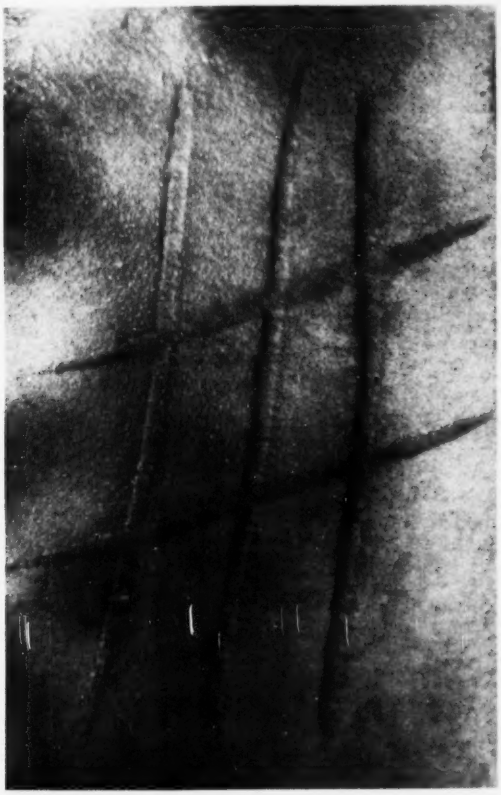

Fig. 4.—Grade IV abnormal response, 30 minutes after stroking.

(*b*) Abnormal Grade I, an erythema which persisted significantly longer than the response elicited from first stroking or longer than five minutes.

(*c*) Abnormal Grade II, an erythematous band occurring immediately after stroking and persisting in most instances over 10 minutes.

(*d*) Abnormal Grade III, a wide erythematous band which occurred within 60 seconds after stroking and which showed an additional pilomotor reflex and/or persistent follicular swellings outside the stroked area.

(*e*) Abnormal Grade IV, fully developed dermographia (triple response).

5. The hematological studies were done by the Department of Pathology, McGill University.

Pretreatment intradermal tests with penicillin and trichophytin were performed in 75 patients, following the technique of Peck and Siegal,[1b] as well as with 1% solution of aqueous procaine.

RESULTS

One patient gave a strongly positive reaction to penicillin, and two reactions were doubtful. All three patients subsequently displayed some untoward side-effect of penicillin therapy. The positive reactions were too few to evaluate this procedure.

Nine positive reactions to trichophytin were seen but no correlation with the incidence of treatment reactions or with the degree of response to stroking was seen.

TABLE 1.—*Response to Stroking in 100 Patients Before Therapy* *

Response	No Previous Penicillin Therapy		Previous Penicillin Therapy	
	No.	Per Cent	No.	Per Cent
Total	76	100	24	100
Normal	61	80.2	3	12.5
Abnormal	15	19.8	21	87.5

* Note should be taken of the significant difference in the incidence of abnormal response to stroking in patients who had previous penicillin therapy and those who gave no history of penicillin medication. The latter group may well include some patients who have had penicillin, either orally or by injection, postoperatively or after childbirth, or who may have used it topically without knowing the nature of the medication.

TABLE 2.—*Change of Skin Response During and After Penicillin Therapy in Sixty-One Patients with Initially Normal Response**

Skin Response	No.	Per Cent
Stayed normal	9	15.4
Grade I	7	11.6
Grade II	26	42.2
Grade III	13	21.1
Grade IV	6	9.7
Total change	52	84.6

* Of these 61 patients 48 were followed for at least 12 months.

In 42 patients abnormal skin response was still present at the end of this period.
Some patients were followed for as long as 24 months and still showed abnormal reaction.
In only six instances skin response returned to normal within one year.
Some of the instances of dermographia persisted unchanged for a period of over two years. The majority of the increased cutaneous responses diminished after a period of 12 to 16 months.
There was no difference in incidence of abnormal reactions or in intensity of abnormal skin response in males and females, and no correlation with the age of the patient or the stage of syphilitic infection was found.

There were three patients with positive reactions to procaine. One of these patients suffered an immediate severe reaction following the fourth injection, which was characterized by thready pulse, drop in blood pressure, suffusion of conjunctivae, and profuse sweating followed by extreme pruritus and cutis anserina.

Serum-Sickness-Like Type of Urticaria.—In three patients a serum-sickness-like type of urticaria occurred, characterized by an initial rise in temperature and subsequent rapid spread of large urticarial lesions, often combined with angioneurotic edema, pain and swelling of the joints, pruritus, and swelling of the palms and the soles. In these patients mild symptoms were observed after the third and fourth injection, followed by sudden severe eruption if another injection was given. We had the impression that the antihistaminic drugs aborted this type of urticaria if given when the initial symptoms were first noted.

One of these patients, in addition to urticarial lesions, showed hemorrhagic bullae which subsided spontaneously after several days, and another displayed lesions of erythema-multiforme type.

Follicular Urticarial Lesions.—This form of urticaria was seen in 13 patients. The lesions varied in size from pinpoint to 2 mm. in diameter, were localized on hair follicles, and were extremely pruritic. Upon stroking, follicular urticaria and

TABLE 3.—*Total Number of Penicillin Reactions in 100 Patients* *

	Males		Females		Total Per Cent
	No.	Per Cent	No.	Per Cent	
Patients with one or more reactions	23	46.4	29	55.6	52
Patients without reactions	25	53.6	23	44.4	48
Total	48	100	52	100	100

* The percentage of patients showing some side-effects of penicillin is much higher in our series than in others, because we listed minor reactions which did not interfere with continuation of therapy. Some of these reactions were found only after careful examination and thorough questioning of the patients.
No correlation to sex or age of patients was seen.
Jarisch-Herxheimer reactions and dermographia are not listed in this table. No correlation between the number or intensity of treatment reactions and changed response to stroking and dermographia was found.

TABLE 4.—*Incidence and Type of Side-Effects After Penicillin Therapy in Fifty-Two Patients Showing One or More Reactions* *

	Males, No.	Female, No.	Total, No.
Patients showing one or more reactions	23	29	52
Urticarial reactions (except dermographia)	14	13	27
Other cutaneous reactions	8	6	14
Respiratory reactions (vasomotor rhinitis, bronchial spasm)	2	5	7
General reactions (fever, malaise)	2	5	7
Total cutaneous reactions (except dermographia)	22	19	41
Total other reactions (except Jarisch-Herxheimer)	4	10	14
Total reactions (except Jarisch-Herxheimer and dermographia)	26	29	55

* It should be noted that there are no statistically significant differences in sex and age distribution of reactions and that several reactions may occur in one person.

TABLE 5.—*Incidence and Type of Urticarial Reactions in 100 Patients Treated with Penicillin* *

Urticaria	Males	Females	Total
Severe, serum-sickness type	2	3	5
Follicular	8	5	13
Pressure type	3	4	7
Localized type	0	2	2
Erythematous swelling of mucous membranes	1	1	2
Total of urticarial lesions	14	15	29

* The follicular type of urticaria was usually attended by dermographia. The other types of urticaria showed no correlation with the response of the skin to stroking, and dermographia was usually absent.

a marked pilomotor response outside of the stroked area was seen in several cases. The sites of predilection were the back, the buttocks, the upper arms, and the thighs. In these patients, marked pilomotor response to stroking was usually elicited several days after the first injection, and with continued therapy a marked follicular dermographia could be demonstrated, and patients complained of severe pruritus. Administration of antihistaminic drugs gave immediate relief of symptoms, but when this treatment was discontinued pruritus often recurred. Intradermal injections with small, increasing doses of histamine phosphate resulted in

permanent relief of symptoms in two patients in whom antihistaminic medication had been of only temporary value.

Penicillin given subsequently, for various indications, to several of these patients caused relapse of symptoms.

The course of this disorder, its onset, and the response to treatment was different from the classic form of penicillin urticaria, and the follicular localization was a distinctive feature suggestive of a different pathogenesis.

Pressure Urticaria.—Seven patients showed a different type of urticarial reaction. The onset was insidious rather than acute, starting with pruritus and minor erythematous lesions. Urticarial lesions developed gradually on pressure points, about the elbows, the hands, the feet, and the buttocks. Pressure and friction from a tourniquet, a tight belt, suspenders, or girdles and even sitting on a hard bench was sufficient to elicit an urticarial wheal confined to the area exposed to pressure. Sites of old trauma, such as scars from boils, showed an increased susceptibility. The pruritus was generally tolerable; in fact, some patients showed multiple urticarial lesions without experiencing any pruritus and without realizing that lesions were present. In general, this type of urticaria responded well to antihistaminic drugs but tended to relapse in some cases when this therapy was discontinued. This reaction occurred usually after the fourth or fifth injection. It

TABLE 6.—*Incidence of Cutaneous Reactions of Nonurticarial Type in 100 Patients Treated with Penicillin*

Flare-Up of Preexisting Cutaneous Diseases	Males	Females	Total
Total	8	6	14
Dermatitis	1	3	4
Seborrhoeic dermatitis	4	1	5
Fungous infections	1	1	2
Other skin diseases (2 acne rosacea, 1 parapsoriasis guttata)	2	1	3

was noted that there was little response to stroking with the tongue depressor in these patients.

Localized Urticaria.—In two patients localized urticaria on the buttocks was seen, appearing in both instances in the form of large urticarial wheals at the site of the first penicillin injection on the right buttock, 24 hours after the second injection was given on the left buttock.

Erythematous Swelling of the Mucous Membrane.—In one patient redness and swelling with pruritus of the vulva was seen, and in another the glans penis was involved. Several similar reactions were seen in patients not included in this series. This may be a localized urticarial reaction, or it may correspond to the hyperemia and edema observed by Blaich [2] on the vulvae of mice.

Preexisting Cutaneous Disorders.—No severe cutaneous reactions of a nonurticarial type were noted in this series, but a marked intensification, spread, or flare of preexisting cutaneous disorders was seen.

Eight patients gave a history or displayed evidence of some form of dermatitis, excluding fungous infections. Six of these showed a marked intensification of their symptoms or a relapse of their condition while receiving penicillin therapy.

Five of six patients with a pronounced seborrhoea of the scalp and face prior to penicillin therapy suffered a marked flare-up of the condition, and in two instances, a widespread dissemination of the seborrhoeic dermatitis occurred.

In two patients acne rosacea was diagnosed prior to institution of therapy. In both instances exacerbation of the condition was observed during penicillin treatment, and one patient with parapsoriasis guttata showed a similar reaction.

Fifty-one male and 22 female patients either gave a history of having dermatophytosis previously or showed clinical signs suggestive of fungous infection. Cultures were not done routinely, and it is likely that some conditions of bacterial origin were erroneously included. Only two patients showed a marked flare-up during treatment. For all patients with clinically suggestive signs of mycotic infection an ointment containing 10% undecylenic acid in a base made with zinc oxide and emulsified glycerin was prescribed. This prophylactic measure may be the reason for the low incidence of activation of mycotic infections, but it could not account for the fact that the incidence of reactions was not higher in the group of patients with a history or clinical evidence of mycotic infection than in the patients without such evidence.

Contact Dermatitis Occurring During the 12-Month-Observation Period.—In five female patients and in two male patients, contact dermatitis occurred during this period. This finding may not be statistically significant, but it seems to bear out our previous observation of the frequent occurrence of contact dermatitis due to a variety of contactants, such as nail polish, rubber, perfume, wool fat, and finishing material and dyes in textiles, as well as dermal reactions to soaps and detergents after penicillin therapy. Many of these patients had no history of previous allergies or skin diseases. We have collected a considerable number of such cases, but have found no way of comparing the incidence of contact dermatitis in penicillin-treated patients and a comparable group of untreated subjects.

Hyperhidrosis.—Thirty-one per cent of all patients showed evidence of hyperhidrosis upon pretreatment examination. An intensification of this condition was noted in all instances, and many patients remarked spontaneously on the increased perspiration. No statistically significant correlation between hyperhidrosis and the incidence of penicillin reactions was found, but it appeared that dermographia and urticaria were more pronounced in these patients. The number of cases was too small for definite conclusions, and no objective measurement of the degree of sweating was attempted.

Respiratory Reactions.—Vasomotor rhinitis and bronchial spasm occurred in seven patients. They complained of general malaise and of a recurring "cold" after each injection of penicillin. Antihistaminic therapy controlled the symptoms.

Pneumonia developed in two patients while receiving therapy. The causative agent was Hemophilus influenzae not sensitive to penicillin in one instance, and in the second patient the condition was diagnosed as an atypical (virus) pneumonia.

General Malaise and Fever.—Seven patients complained of fever and malaise after the third (1 patient), fourth (4 patients), and fifth (2 patients) injections. Care was taken not to include Jarisch-Herxheimer reactions under this heading. These patients complained of fever, malaise, chills, weakness, excessive sweating, and, in some instances, marked thirst. The peak of the temperature was at night and could not be determined accurately. Of interest was the fact that all these patients had unusually high penicillin-serum levels on the third and fourth day after the last injection, at which time the reaction occurred.

HEMATOLOGIC STUDIES

A complete hemogram was performed on 21 patients, 10 men and 11 women. Nine of these patients gave a history of previous penicillin therapy.

Patients who had had previous penicillin therapy showed a significantly higher initial eosinophile count than the untreated group. Both groups showed an increase in the number of eosinophiles after completion of the course of penicillin therapy. This increase started after the first injection and progressed with each injection, except for five patients in whom a temporary, sudden drop in eosinophiles occurred concomitant with a treatment reaction. This was observed in four patients with urticaria and in one instance of general malaise. The highest number of eosinophiles, on the other hand, occurred in a patient with an urticarial reaction, probably of an allergic nature. In this instance, an eosinophilia of 1,426 (19.75%) was noted. The increase in eosinophiles and a shift to the left in the differential count during penicillin therapy was confirmed in 25 additional patients for whom a count of white blood cells and a differential count was done.

Fourteen patients showed a slight increase in fragility of the capillaries during treatment. The sedimentation rate increased significantly in five instances, and this increase was correlated with a treatment reaction in every case.

The leucocytes showed a rather capricious behavior. In six patients the white blood cell count remained unchanged (about 7,000) during therapy, while in 10

TABLE 7.—*Results of Hematologic Study of Twenty-One Patients Treated with Penicillin*

	Patients, No.	Eosinophiles, Average No.		Increase, Per Cent
		Before Penicillin	After Penicillin	
Previous penicillin therapy	9	422	549	30
No previous penicillin therapy	12	171	358.7	109.4
Total	21	278	434.5	56.4

patients with an initially high count (9,000 and above) a slow decrease was observed. In three instances an increase of over 50% occurred, and an increase of over 100% was seen in one patient, concomitant with an outbreak of urticaria. A sudden drop in the number of leucocytes occurred in four patients, all showing an urticarial reaction. The number of polymorphonuclear neutrophiles varied proportionately with the changes in total count. However, regardless of whether leucocytosis or leucopenia was present, the number of rod forms increased two to three times during therapy.

The number of lymphocytes varied with different patients. In 10 patients a slight increase after the second or third injection and a subsequent return to the initial value was noted, while in 11 instances a drop in lymphocytes occurred. Most patients who had had previous penicillin therapy or who showed treatment reactions were in this group. In one instance marked lymphopenia was noted (a drop from 1,906 to 990 per cubic millimeter). An urticaria occurred at this time.

COMMENT

Over 80% of the patients in our series showed an increase in vascular response to stroking the skin, which heretofore was reported by Stokes[6] and one of us

6. Stokes, J. H.: Action of Penicillin in Late Syphilis, Including Neurosyphilis, Benign Late Syphilis and Late Congenital Syphilis: Preliminary Report, J. A. M. A. **126**:73 (Sept. 9) 1944.

after penicillin treatment.[7] An increased erythema or a true dermographia is not commonly seen as a symptom of allergic sensitization, and these phenomena cannot be produced experimentally with any regularity by a specific sensitization. The very high percentage of increased vascular response to stroking noted in our series was in itself a feature suggestive of a mechanism other than specific sensitization to penicillin.

We have already quoted Blaich,[2] who found increased activity of organs under cholinergic control after penicillin, and who demonstrated capillary dilatation and increased permeability, and we have made reference to Goetz,[3] who showed increased whealing and erythematous response after small doses of penicillin. It is possible that the increase in vascular response to stroking observed in our series was caused by a similar mechanism.

The flare-up of acne rosacea and of seborrhoea is equally suggestive of an increase in capillary sensitivity rather than of a specific sensitization. That penicillin may act as a vascular stimulant is also suggested by its beneficial effect on acrodermatitis atrophicans, which has been reported by many authors including Svartz,[8] Miescher,[9] and Thyresson.[10]

Most authors consider acrodermatitis a trophic vascular disorder rather than a bacterial disease. Haxthausen [11] transplanted diseased skin into normal skin areas and covered the operative skin defect with normal skin. The normal skin graft showed progressing atrophy within a few weeks, while the diseased transplant became normal within a short period. He concluded from these experiments that the beneficial effect of penicillin in acrodermatitis was due to some effect other than its bacteriostatic or bactericidal action.

These observations, the literature on this subject, and our own observations suggest a nonspecific, drug-like action of penicillin in some instances, probably a cholinergic stimulation. The mechanism of such a supposed stimulation is unknown. It may be central, or penicillin may exert a direct influence on nerve endings, or it may be due to an increased muscular response to cholinergic stimulation. Further theoretic possibilities might include an increase in acetylcholine formation or an inhibition of cholinesterase. Torda and Wolff,[12] however, have demonstrated that penicillin does not inhibit cholinesterase, that, on the contrary, acetylcholine formation appeared to be reduced. They found, on the other hand, that penicillin increases the potassium sensitivity of muscles.

Our observations of increased perspiration after penicillin may also be interpreted as a cholinergic stimulation, as the sweat glands, while anatomically

7. Kalz, F.: Dermographia, Another Side Effect of Penicillin Therapy, Arch. Dermat. Syph. **54**:66 (July) 1946.

8. Svartz, N., cited by Thyresson, N.: Acta dermat.-venereol. **29**:572, 1949.

9. Miescher, G.: Die Behandlung der Akrodermatitis atrophicans mit Penicillin, Dermatologica **98**:59, 1949.

10. Thyresson, N.: Penicillin Treatment of Acrodermatitis Atrophicans Chronica (Herxheimer), Acta. dermat.-venereol. **29**:572, 1949.

11. Haxthausen, H.: Studies on the Pathogenesis of Morphea, Vitiligo and Acrodermatitis by Means of Transplantation Experiments, Acta. dermat.-venereol. **27**:352, 1947.

12. Torda, C., and Wolff, H. G.: Effect of Penicillin and Sulfonamides on Acetylcholine Synthesis and Response of Muscle to Acetylcholine and Potassium, J. Lab. & Clin. Med. **31**:650, 1946.

innervated by sympathetic fibers, do respond to cholinergic stimulation. Ormea [13] has recently demonstrated that a direct continuity exists between the terminal network of autonomous nerve fibers of capillaries, sweat glands, and sebaceous glands and the smooth muscular fibers of the arrectores pilorum.

The persistence of an increased response to stroking, or true dermographia over a period of many months, even years, is not explained by any of the possibilities mentioned above and appears to us the most puzzling phenomenon. It is known that highly toxic substances, such as botulinus toxin, may cause a permanently changed vascular response. Similar changes have also been observed after high doses of x-rays. As penicillin is certainly not a toxic substance and as permanent damage to the capillaries cannot, therefore, be assumed, one may have to refer to such a vague term as protracted or permanent vagotonia of the superficial vessels of the skin to explain this phenomenon.

The possibility that some of the urticarial lesions observed in our series were due to a change in capillary permeability must be considered. Grant, Pearson and Comeau [14] described a number of patients in whom urticaria occurred with warming of the body, after exercise, and with emotional stress, and they demonstrate the mechanism of this reaction in careful experiments. They produced urticaria by injection of pilocarpine and inhibited the outbreak with atropine sulfate, and they believed that acetylcholine was set free under cholinergic stimulation, which in turn caused release of histamine which was instrumental in producing the whealing effect.

Graham and Wolf [15] recently reviewed some of the extensive literature on urticaria associated with stressful life conditions. They examined 30 patients with repeated attacks of urticaria, angioneurotic edema, and dermographia and found absence of allergic factors and a definite correlation with a particular type of emotional stress. The experimental part of this paper was of interest. The reactive-hyperemia threshold was measured as well as skin temperatures, and it was found that both arterioles and capillaries dilated during stressful interviews. In all patients with urticaria some dermographia and urticarial lesions occurred at sites of friction, under the belt, collars, and shoulder straps. As mentioned above, dermographia and urticaria on pressure points and areas exposed to mechanical friction was also a finding in our series.

Lewis,[16] in his classic experiments, has demonstrated the importance of cutaneous vascular changes for the production of wheals, and Ponder [17] believed that dilatation of capillary vessels automatically caused increased permeability.

13. Ormea, F.: Sull'innervazione vegetativa della cute umana: Generalità sull'innervazione della pelle, Minerva med. **1**:118, 1950.

14. Grant, R. T.; Pearson, R. S., and Comeau, W. G.: Observations on Urticaria Provoked by Emotions, by Exercise and by Warming the Body, Clin. Sc. **2**:253, 1936.

15. Graham, D. T., and Wolf, S.: Pathogenesis of Urticaria, J. A. M. A. **143**:1396 (Aug. 19) 1950.

16. Lewis, T., and Grant, R. T.: Vascular Reaction of the Skin to Injury: The Liberation of a Histamine-Like Substance in Injured Skin: The Underlying Cause of Factitious Urticaria and of Wheals Produced by Burning, and Observations upon the Nervous Controls of Certain Diseases, Heart **11**:209, 1924.

17. Ponder, E.: The Capillaries and the Lymphatics, in Fulton, G. F.: Textbook of Physiology, Ed. 16, Philadelphia, W. B. Saunders Company, 1949.

Summarizing the experimental and clinical evidence on this question, one may state that dilatation of the capillaries caused by an allergic mechanism, an emotional stimulus, or a cholinergic drug, such as pilocarpine or acetylcholine, may cause urticaria in susceptible persons. The work of Blaich [2] and of Goetz [3] demonstrates that penicillin has a stimulating effect upon the cholinergic fibers and causes hyperemia and increased capillary permeability. Grant and other authors have shown that heat, emotional stimuli, and other factors may cause the same effect, possibly by increased acetylcholine output. We suggest, therefore, that in the large number of cases of changed skin response and of dermographia, as well as in the cases of pressure urticaria observed after penicillin therapy in our series there may be a similar mechanism as the pathogenetic factor. The follicular urticaria could also be explained by an increased acetylcholine activity about the hair follicles.

We do not suggest that in all cases urticaria after penicillin therapy is due to an unspecific effect of penicillin. The serum-sickness type of delayed urticaria and the localized type at the site of injection are probably examples of an allergic reaction.

Vasomotor rhinitis is probably due to specific sensitization. We have no suggestion regarding the pathogenesis of fever and malaise observed in some of the patients.

The question of an increased susceptibility to contact sensitization following penicillin remains unanswered. The incidence of contact dermatitis in 7% of the patients within one year after administration of penicillin appears high and seems to bear out our previous observation of an increased incidence of contact dermatitis after penicillin. The absence of a comparable series of untreated persons prevents a statistical evaluation of these findings.

Role of Histamine and Effect of Antihistaminic Drugs.—The prompt effect of antihistaminic drugs upon urticaria in some patients and upon other penicillin reactions suggests that histamine plays some role in the pathogenesis of these disorders. This neither proves nor disproves an allergic mechanism. Grant [14] demonstrated the role of histamine in some of his cases of cholinergic heat urticaria, and it is well known that nonspecific stimuli such as heat or cold may cause the release of histamine from the skin. Of interest was our observation that antihistaminic drugs were effective in some of our patients but quite ineffective in others. This parallels the observations of Rose [18] on urticaria due to cold. He demonstrated that in most cases histamine occurs in large quantities in the venous blood of hands and forearms immersed in cold water, while in some cases no increased histamine values were found. The former group reacted favorably to antihistaminic therapy, while no effect was observed in the latter. It is quite possible that acetylcholine may cause an urticarial reaction directly without mediation of histamine in these cases.

Hematological Changes.—Our findings of an increase in the number of eosinophiles after penicillin treatment were equally difficult to interpret. Eosinophilia has been previously reported by Lyons,[19] who attributed it to the impurities in the

18. Rose, B.: Studies on the Role of Histamine in Hypersensitivity to Cold, J. Clin. Invest. **27**:553, 1948.

19. Lyons, C.: Penicillin Therapy of Surgical Infections in U. S. Army, Report, J. A. M. A. **123**:1007 (Dec. 18) 1943; personal communications to the authors.

first penicillin preparation, and by Mosonyi.[20] The question of eosinophilia was discussed in a recent editorial in the *Annals of Internal Medicine*.[21] Causes of eosinophilia were listed as follows: allergic diseases, various dermatoses of unknown origin, infections, infestations, malignancies, Hodgkin's disease, some collagen diseases, a variety of bone diseases, irradiation therapy, and drugs (emetine hydrochloride, liver injection, arsenic, trimethadione [tridione®], iodides, digitalis, heavy metals, penicillin, and streptomycin). In this article the author concluded that eosinophilia is often related to the presence of a foreign or abnormal protein. Several others are cited who have shown that epinephrine and cortisone caused eosinopenia, and an article by Godlowski is mentioned in which it was suggested that eosinophilia was a "vagal reaction" while eosinopenia was a "sympathetic" reaction. It appears, therefore, that the presence of eosinophilia *per se* is of no value in distinguishing between an allergic reaction and the assumed vagal stimulation. The sudden drop of eosinophiles at onset of urticaria is analogous to the eosinopenia observed in some acute asthmatic attacks.

The weight of evidence supports an allergic mechanism in some cases of penicillin reaction, such as the delayed serum-sickness type of urticaria, urticaria at the site of injection, and vasomotor rhinitis, while dermographia, pressure urticaria, and perhaps the follicular type of urticaria may be due to a drug-like effect of penicillin.

SUMMARY

One hundred unselected patients receiving penicillin therapy were observed with regard to treatment reactions. Their responses to stroking with a blunt instrument were listed.

The intensity of the cutaneous response to stroking increased in 80% of the patients; in 10% true and persistent dermographia developed after therapy.

In 53% of all cases there were some side-effects of penicillin, not counting Jarisch-Herxheimer reactions and dermographia. There were cutaneous reactions in 41% and respiratory and general reactions in 14%.

Seborrhoea, acne rosacea, and some other preexisting cutaneous disorders were aggravated by penicillin treatment.

No correlation of the reactions with sex, age, or mycotic infection was found.

Eosinophilia occurred regularly in all patients, as well as a shift to the left in the neutrophile leucocytes.

Two variant types of urticarial lesions have been described: (*a*) urticarial swellings limited to areas exposed to pressure, and (*b*) small urticarial lesions limited to the sites of hair follicles.

The literature on the effect of penicillin upon the autonomous nervous system has been reviewed and the pathogenesis of the various types of reactions discussed.

Evidence has been presented suggesting that some of these reactions may be due to cholinergic stimulation rather than to a specific sensitization.

1414 Drummond St.

20. Mosonyi, L., and Oblatt, E.: A propos des phénomènes allergiques survenus aux cours du traitment antibiotique de long durée, Schweiz. med. Wchnschr. **79**:104, 1949.

21. Some Observations on the Eosinophil, editorial, Ann. Int. Med. **33**:1054, 1950.

PRE-L. E. CELL: A STAGE IN DEVELOPMENT OF THE L. E. PHENOMENON

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FREDERIC FELDMAN, M.D.
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MAURICE MORRISON, M.D.
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THE PURPOSE of this paper is to describe and illustrate a new, bizarre cell which may be one of the stages in the formation of the L. E. cell. Recognition of this cell may help in the establishment of an early diagnosis of disseminated lupus erythematosus.

HISTORICAL SUMMARY

The original report in 1948 by Hargraves and his associates[1] of the finding of a new cell, the L. E. cell, in the bone marrow of patients with acute disseminated lupus erythematosus stimulated a great deal of interest and research into the mechanism of the formation of this cell. An ever-increasing number of studies by many different groups of workers has been constantly appearing in the literature. A summary of the findings to date follows:

1. The L. E. cell and its related cytological abnormality, the L. E. rosette, are specific for the disease acute disseminated lupus erythematosus.[2] However, a few false-positive tests have been reported.[2b]

2. The inclusion body in the L. E. cell consists chemically of partially depolymerized desoxyribose nucleic acid and is derived from altered nuclear substance.[2b]

3. The L. E. phenomenon (L. E. cells and/or rosette formation) can be found in the bone marrow or peripheral blood of patients with the specific disease.[3] It

From the Hematology Service, Jewish Hospital.

1. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25 (Jan. 21) 1948.

2. (*a*) Haserick, J. R.: Plasma L. E. Test in Systemic Lupus Erythematosus: Study of 23 Patients with Positive L. E. Tests, J. A. M. A. **146**:16 (May 5) 1951. (*b*) Lee, S. L.; Michael, S. R., and Vural, I. L.: The L. E. (Lupus Erythematosus) Cell: Clinical and Chemical Studies, Am. J. Med. **10**:446 (April) 1951.

3. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus: Report on the Hargraves' "L. E." Cell, J. Invest. Dermat. **11**:209 (Sept.) 1948. Sundberg, R. D., and Lick, N. B.: "L. E." Cells in the Blood in Acute Disseminated Lupus Erythematosus, ibid. **12**:83 (Feb.) 1949.

can also be produced in the bone marrow or peripheral blood of non-L. E. persons,[4] or the bone marrow of dogs,[2a] by the addition of L. E. plasma.

4. The factor causing the L. E. phenomenon is in the gamma-globulin fraction of plasma.[5] The gamma-globulin fraction in acute disseminated lupus erythematosus is capable of producing antibodies (in rabbits) which can precipitate the L. E. factor, while antibodies against normal gamma-globulin plasma fraction fail to do so.[6] Thus it is apparent that L. E. gamma globulin differs immunologically from normal gamma globulin.

5. The L. E. phenomenon can be produced with or without the addition of anticoagulants to the blood or bone marrow. One essential factor in its production, though, seems to be incubation of the collected specimen before study. An exception to this is Stich's [7] report of a case in which L. E. cells were found independently in 1946, the slide being a direct, immediate smear of bone marrow without any incubation, anticoagulants, or centrifugation.

CLINICAL STUDIES

In the past year we have studied seven patients with acute disseminated lupus erythematosus, and in six we were able to demonstrate the L. E. phenomenon upon admission examination. In the seventh case, which led to this report, this finding was not revealed on first examination. The clinical picture in this case, though, was very definitely and characteristically that of acute disseminated lupus erythematosus, and therapy with cortisone produced a dramatic response. The patient was discharged with an oral maintenance dose of this drug, but, because of the development of edema, the medication was shortly discontinued. A marked clinical relapse brought the patient back into the hospital, and at this time, six weeks after the first unproductive examination, the L. E. phenomenon was present. Typical L. E. cells and rosette formation were observed, (Figs. 1 and 2) but, in addition, all stages in L. E.-cell development were in evidence.

STAGES IN THE FORMATION OF PRE-L. E. AND L. E. CELLS

The following stages in the development of L. E. cells were evident:

Stage 1. Normal polymorphonuclear cells.

Stage 2. Polymorphonuclear cells with one or more lobes becoming slightly pyknotic.

Stage 3. Polymorphonuclear cells with all lobes pyknotic and one or more becoming rounded, the filaments connecting the lobes still intact.

Stage 4. The pre-L. E. cell: Disappearance of the interlobar filaments leaving cells containing normal polymorphonuclear cytoplasm and granules and one to five round, homogeneous, deeply staining masses of nuclear-lobe material (Figs. 3 and 4).

Stage 5.—One or more of the round nuclear masses partially extruded from the cells.

4. Haserick, J. R., and Bortz, D. W.: Normal Bone Marrow Inclusion Phenomena Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**:47 (Aug.) 1949. Hargraves, M. M.: Production in Vitro of the L. E. Cell Phenomenon: Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **24**:234 (April 27) 1949.

5. Haserick, J. R.; Lewis, L. A., and Bortz, D. W.: Blood Factor in Acute Disseminated Lupus Erythematosus: I. Determination of Gamma Globulin as Specific Plasma Fraction, Am. J. M. Sc. **219**:660 (June) 1950.

6. Haserick, J. R., and Lewis, L. A.: Blood Factor in Acute Disseminated Lupus Erythematosus: II. Induction of Specific Antibodies Against L. E. Factor, Blood **5**:718 (Aug.) 1950.

7. Stich, M. H.: The "L. E." Cell in the Bone Marrow in Disseminated Lupus Erythematosus, New York J. Med. **50**:433 (Feb. 15) 1950.

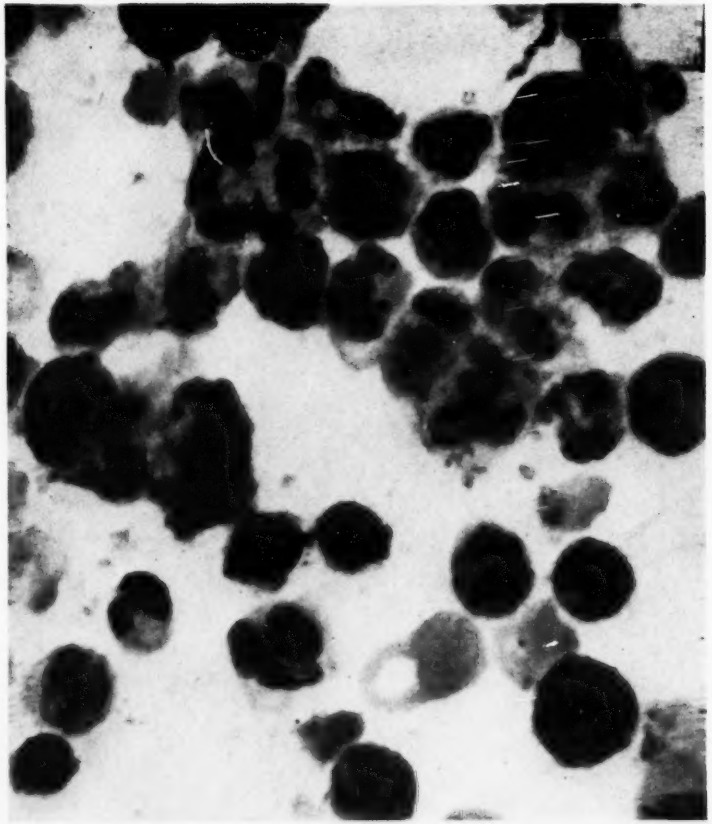

Fig. 1.—L. E. cell and L. E. rosette formation.

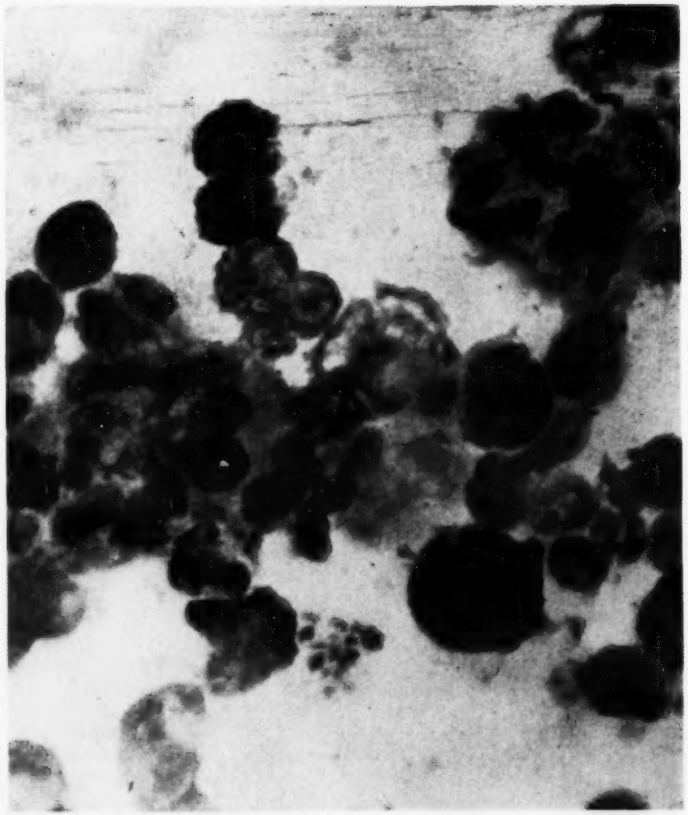

Fig. 2.—Two characteristic L. E. rosettes.

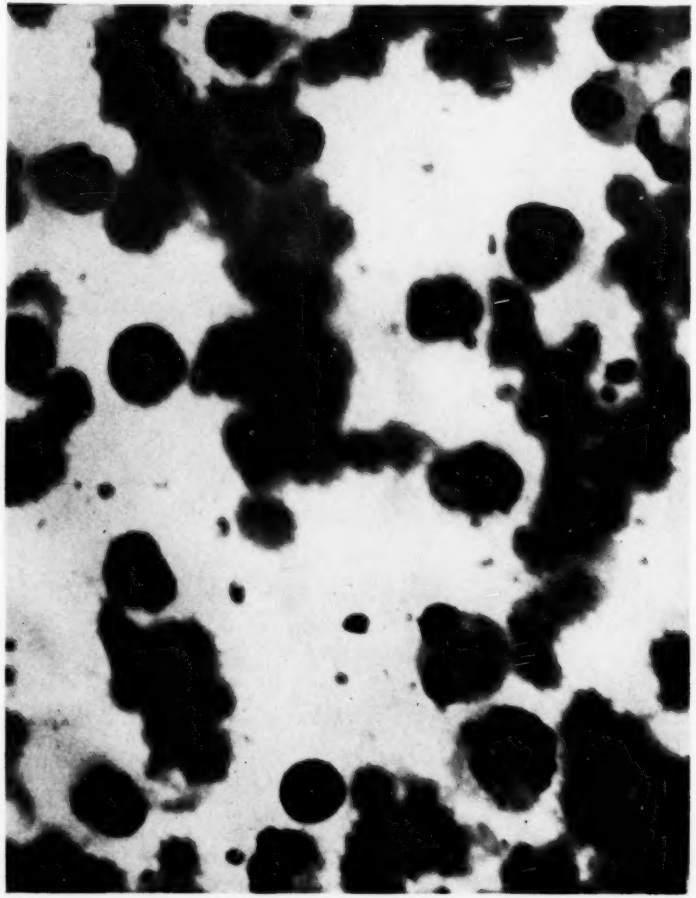

Fig. 3.—Two pre-L. E. cells, one containing five intracellular masses, the other, two. Note that some of the nuclear bodies are partially extruded from the cells.

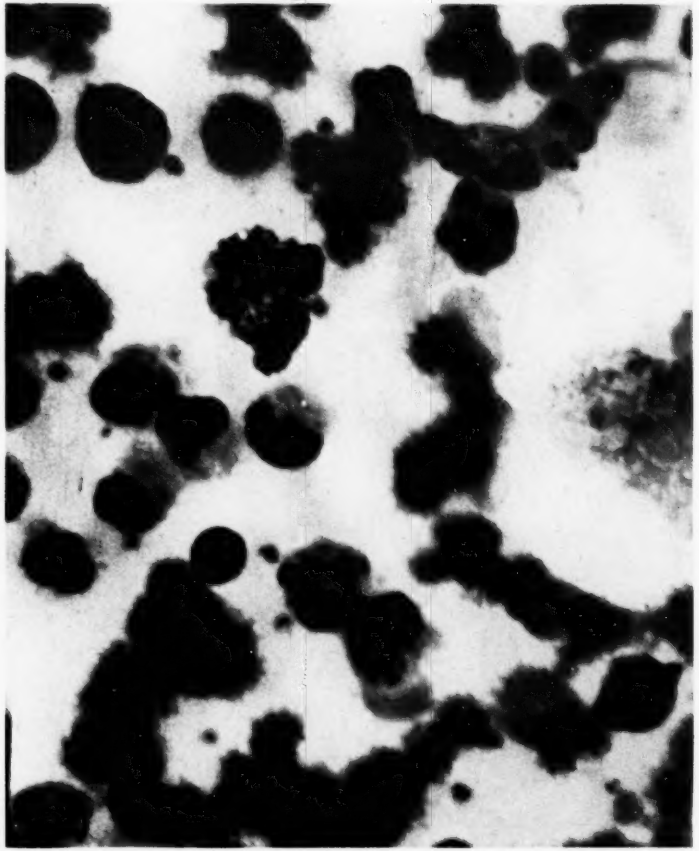

Fig. 4.—Numerous pre-L. E. cells in one microscopic field.

Stage 6. Free lobar nuclear masses.

Stage 7. The L. E. cell: Normal polymorphonuclear cells with a free nuclear mass phagocytosed.

COMMENT

The stages listed above, we believe, demonstrate the actual process in the formation of the L. E. cell. The nucleus of a normal polymorphonuclear cell

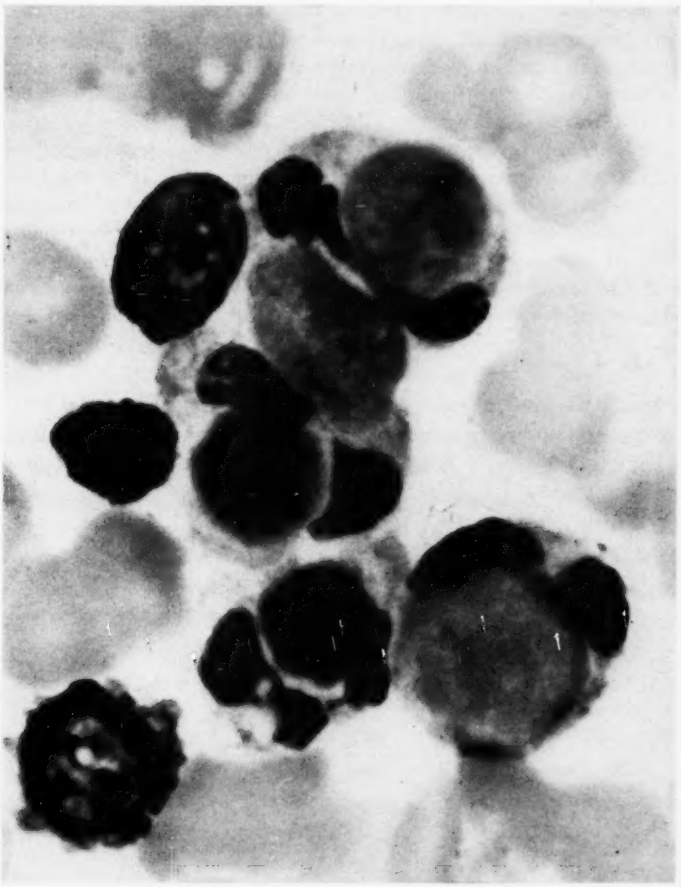

Fig. 5.—A group of L. E. cells. Note the increasingly pale and eosinophilic staining of the inclusion bodies as they become larger.

gradually breaks down under specific chemical and/or immunological influences. It first becomes pyknotic, then fragmented, and, finally, its fragments are extruded from their cell of origin. Another polymorphonuclear cell, circulating in the blood stream and performing its normal function of phagocytosis, comes upon one of these foreign masses of nuclear substance and ingests it exactly as it would any other foreign material.

The pre-L. E. cell is the distinctive stage in this process in which the destroyed fragment of nuclear origin is still within its own cell boundaries. The L. E. cell is the stage in which the nuclear substance has been picked up by another polymorphonuclear cell.

Possibly this panoramic view of the complete process is seen here for the first time because the disease was at a stage in which the activating influence was first becoming effective. One would suspect this from the complete failure to find any evidence of the L. E. phenomenon six weeks previously.

In reviewing our material from previous cases revealing the L. E. phenomenon, we were able in two cases to find an occasional scattered pre-L. E. cell also present, but in nothing like the large number found in the case under discussion. Study of slides from this and other patients has also demonstrated the remainder of the process of formation of the very large phagocytosed masses one finds in L. E. cells. The small ones stain deeply and in a manner similar to the lobes of the ingesting polymorphonuclear cell. As they enlarge, they become increasingly paler and more eosinophilic in color, compressing the nucleus of the ingesting cell to a thin marginal comma-like strand and in occasional cases seeming actually to extrude all or part of it from the cell. In other instances, extremely large masses break through the cell membrane and are partly outside the cell boundaries (Fig. 5).

SUMMARY

A new cell, the pre-L. E. cell, is described and illustrated.

The complete step-by-step process in the formation of the L. E. cell is visualized.

Recognition of the pre-L. E. cell may help in the early diagnosis of disseminated lupus erythematosus.

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SENSITIVITY TO RUBBER MATERIALS

An Analysis of One Hundred Twenty-Five Cases of Eruptions Proved to Be Caused by Rubber Articles

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THE USES of rubber have increased enormously since Goodyear, as the legend goes, tossed a piece of the raw material on a hot stove and was astounded at the bouncing result. By now rubber is indispensable for modern living and comfort, but, like many another invaluable thing, it has some hazards. One of these is its capacity to sensitize the human skin sometimes and then to provoke eczematous eruptions upon subsequent contact.

Many sporadic cases of allergic eczematous contact-type dermatitis from rubber products and even some fairly large series of cases have been reported in the past.[1] The reasons for publishing this paper on the subject are as follows: 1. It seems to us that the absolute number of cases of sensitivity to rubber materials and of eruptions from them is growing huge. 2. So large a series as this is instructive of the variety of uses of rubber and of the many sites of the skin that may suffer (or enjoy) contact with rubber.

The accompanying table is a compilation of some data on 125 cases of proved sensitization to rubber articles and eruptions from them. This series was gathered from cases of patients seen at the New York Skin and Cancer Hospital and in private practice over a period of about five years. It does not begin to exhaust the possibilities but does give some indication of what rubber materials can do dermatologically and where they can do it.

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1. (*a*) Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1947, p. 515. (*b*) Furman, D.; Fisher, A. A., and Leider, M.: Allergic Eczematous Contact-Type Dermatitis Caused by Rubber Sponges Used for the Application of Cosmetics, J. Invest. Dermat. **15**:225 (Sept.) 1950. (*c*) Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice, Ed. 3, Chicago, The Year Book Publishers, Inc., 1948, p. 94. (*d*) Leider, M., and Furman, D.: Allergic Eczematous Contact-Type Dermatitis from Odd Things or in Odd Ways, Ann. Allergy **6**:693 (Nov.-Dec.) 1948.

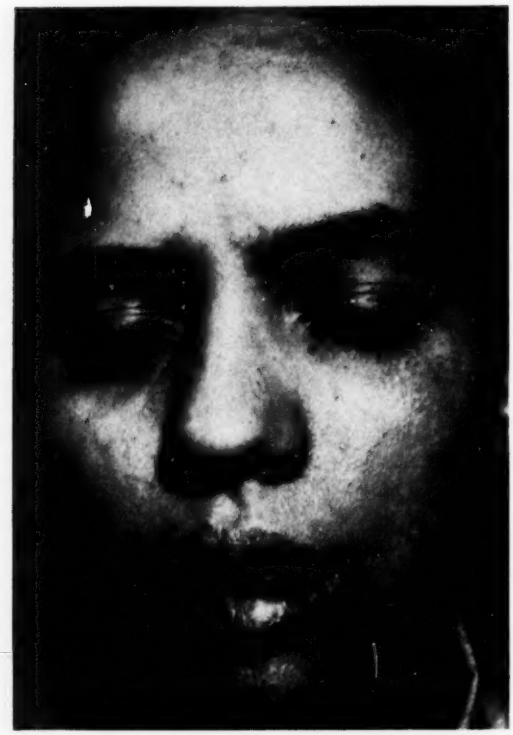

Fig. 1.—Eruption from rubber in a sponge used for application of cosmetics.

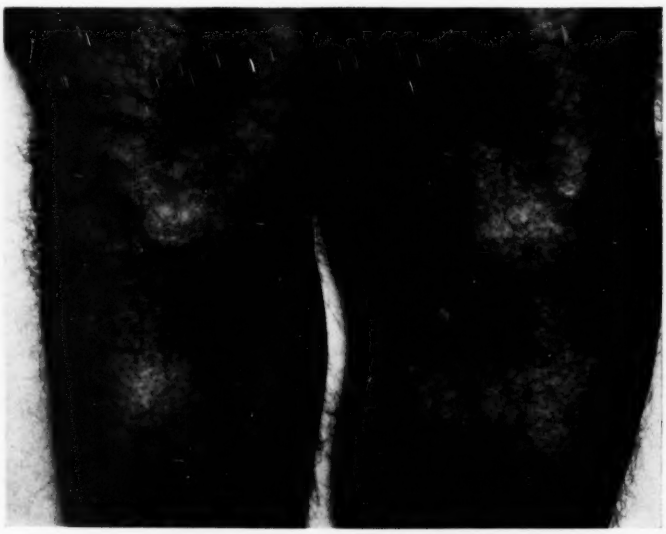

Fig. 2.—Eruption from rubber in men's garters.

Fig. 3.—Eruption from rubber in a girdle.

Fig. 4.—Eruption from rubber in rubber bands.

Fig. 5.—Eruption from rubber in finger guards.

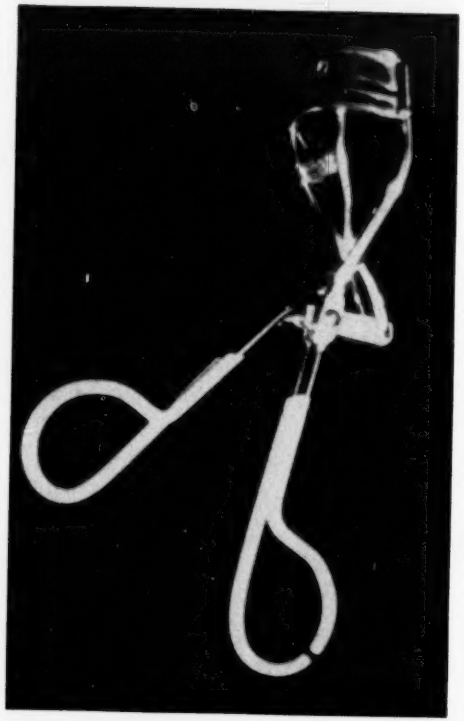

Fig. 6.—Eyelash curler, nickel-plated and tipped with rubber.

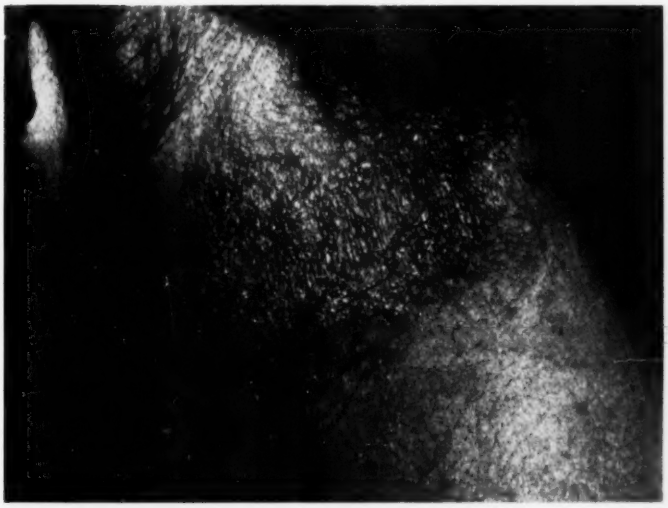

Fig. 7.—Eruption from rubber in headrest of a shampoo tray.

Fig. 8.—Eruption from rubber in a bathing cap.

Fig. 9.—Eruption from rubber in the hand grip of a barber's vibrator.

Fig. 10.—Eruption from rubber in a pad on a sewing machine operated by pressure with the outer knee. Kneeling-pad eruptions are similar except for patellar location.

Distribution of 125 Cases of Eruptions Caused by Rubber Products

Type of Rubber Product	No. of Cases	Comment
Rubber sponges used for application of cosmetics	40	Part of this series has been reported previously.[1b] The article cited should be consulted for pertinent clinical and other phenomena about eruptions from this source (Fig. 1)
Rubber gloves	17	This is one of the most obvious and best known examples of rubber sensitivity
Rubber in predominantly nonrubber garments (*a*) Elastic on shoes (*b*) Elastic on shorts (*c*) Elastic in hair nets (*d*) Garters (*e*) Girdles (*f*) Brassieres (*g*) Dress shields	21	Dermatitides of the feet frequently are troublesome diagnostic and therapeutic problems. Definitive proof of cause of trouble from rubber (or nonrubber allergens) is always gratifying. On other parts of the body incrimination of rubber or other allergenic materials may or may not be as obvious as it sometimes is on the feet. When rubber cannot, in such cases, be proved by patch tests or tests of avoidance and reexposure to be causative, then some other more or less common allergen should be sought or some other condition, such as lichen chronicus simplex, should be considered. This is particularly true in lichenified appearances under brassieres and girdles (Figs. 2 and 3)
Condoms	6	Condom rubber as a cause of dermatitis of the penis should be obvious but is either less well known or less publicized than it should be. We have even seen one patient with rare leucoderma of the penis from agerite alba in condom rubber, and while this effect is probably not a sensitization phenomenon, we mention it out of general interest and because it is such an odd instance of "leucopenia"
Rubber bands	5	One patient showed the eruption on the wrist from the common practice of carrying rubber bands in this fashion (Fig. 4). In other cases the eruption was on the lower thighs from use of rubber bands as garters. A similar illustration appears in footnote 1 *b*
Rubber dental plates	5	Stomatitides also are difficult diagnostic and therapeutic problems. Proof of rubber sensitivity is rewarding because of the availability of substitute materials
Rubber kneeling pads	4	Three of these cases were in housewives who used these popular aids in floor scrubbing. The other case is of special interest because it was unilateral. The patient was a devout churchgoer who used the pad in prayer and, being arthritic, could genuflect on but one knee
Rubber panties	3	Implication of rubber or other waterproof materials is usually obvious in cases of this sort. The patients generally are children. Failing absolute proof of sensitization one must consider and seek some other cause of dermatitis of the region
Rubber finger guards	3	This exposure is usually occupational in file clerks. It is important because eruptions on the fingers, like those in the mouth and on the feet, are often difficult diagnostic and therapeutic problems. This eruption frequently appears psoriasiform (Fig. 5)
Rubber edge on eyelash curler	3	Dermatitis of the eyelids is most commonly due to sensitivity and exposure to nail polish. In the 10 to 15% of cases that are not due to nail polish, but that are still contact allergic eczemas, other and more obscure allergens may be causative. Nickel, in our experience, is next most often the culprit. In one of our cases, the patient was sensitive to both rubber and nickel. The instrument is illustrated in Fig. 6
Rubber headrest	2	A kidney-shaped rubber headrest is attached to the shampoo tray used in many beauty parlors. The sides of the neck and the nuchal area receive contact and show dermatitis (Fig. 7)
Rubber bathing cap	2	Distribution of the eruption and a positive history of use is usually suggestive of rubber. Proof by patch test and avoidance is usually easy (Fig. 8)
Rubber dental dams	2	In certain dental procedures fine rubber sheeting is used to isolate the work area. The rubber frequently is stretched across the face and held in place by a mechanical device. In one of our patients leucoderma developed in addition to dermatitis

Distribution of 125 Cases of Eruptions Caused by Rubber Products—Continued

Type of Rubber Product	No. of Cases	Comment
Rubber supportive pessary	1	A 65-yr.-old woman was found to have a stomatitis from a rubber dental plate. Upon investigation for incidental pruritus vulvae and vaginitis, it was discovered that she was wearing a doughnut-type rubber supportive pessary. Reaction to patch test with a portion of this pessary was strongly positive. Soon after removal of the pessary the pruritus and vaginitis disappeared
Rubber toy	1	The patient was a child, and the cause was not quickly obvious
Rubber apron (bib)	1	In cases of this sort the cause would not be as readily obvious as rubber-panty dermatitides
Rubber button on headpiece of hearing aid	1	The cause was obvious from the construction and manner of use of the device. Proof was easy by reversing the headpiece so that the rubber button came to rest on the other side of the head. This virtual patch test resulted in the appearance of the eruption on the opposite side of the head
Rubber mammary prosthesis	1	The cause was fairly obvious from the location and the volunteered history. It has been previously reported [1d]
Rubber goggles	1	The cause was obvious from the location and history
Miscellaneous occupational contact with rubber	6	These are samples from a small experience with industrial cases. There were toy fabricators, barbers, and a seamstress. The cases of barbers are of particular interest because the dermatitis was derived from the hand grip of vibrators. The dorsum of the manipulating hand showed a broad band of dermatitis that corresponded to the manner in which the hand slipped into the grip to guide the instrument (Figs. 9 and 10)

COMMENT

In all cases recounted in the table the dermatitides were proved to be caused by rubber materials by history of use, by patch tests, and by tests of restoration to normal when the particular rubber product incriminated was avoided. Identification of precise allergens in the various rubbers was not attempted because, from the nature of rubber, it was hardly likely that such investigation would be fruitful. A recent query [2] of one of the largest rubber producers revealed that between 1,000 to 1,500 different chemical entities go into the production of finished rubber. Moreover, there are many varieties of rubber, and the end-product of rubber manufacture seems to result in substances that are different from any of the component parts.

In the event of sensitization to a rubber article, elimination of it from direct cutaneous contact is the best and only definitive treatment. When use and contact with rubber appears unavoidable (e. g., rubber gloves among surgeons), trial of different brands may be rewarded by discovery of makes that are tolerable. Occult sources of rubber contact (adhesive tape, rubber cements, etc.) may pose problems in recalcitrant allergic contact eczemas that are surely due to rubber ingredients, and it may tax detective ingenuity to uncover and eliminate them.

Despite the fairly large size of this series, rubber cannot be said to have a high index of sensitizing potential. In fact, considering the large number, frequency, and continuity of rubber contacts, its sensitizing potential must be relatively low. While the actual mechanism of allergic sensitization is in general unknown, it can still be said that the number of clinical episodes must be a function of sensitizing capacity times the number and quality of contacts. In the case of rubber, the

2. United States Rubber Company: Personal communication to the authors.

absolute number of cases appearing must vary directly with the contact (use) rate, since this is the important variable, whereas its sensitizing potential is fixed and small.

SUMMARY

Some features of 124 cases of sensitivity to rubber and eruptions from it are reported.

As in most cases of allergic eczematous contact-type dermatitis, treatment involves strict avoidance of the offending substance. In rubber sensitivity it is sometimes possible to obtain substitutive products because of the great variety in composition.

Specific allergens in rubber are not readily discoverable because of the complex nature of the material, but the sensitizing potentials of whatever substances there are in rubber that can sensitize must be low, considering its wide and generally harmless use.

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SEBORRHEIC KERATOSES

Are They Delayed Hereditary Nevi?

A. J. REICHES, M.D.
ST. LOUIS

SEBORRHEIC keratoses, sometimes designated as verrucae seniles, seborrheic warts, pigmented papillomas, or verrucae pigmentosae, are relatively benign lesions which should be differentiated from precancerous senile keratoses. Seborrheic keratoses are sharply circumscribed, oval or round elevations, varying in size from 0.25 to 3 cm. These lesions are flat and multiple, but as their size increases they sometimes become pedunculated and covered with a greasy, friable scale. Common sites are the chest, interscapular region, waistline, and face. Early lesions are grayish-yellow; older lesions become yellowish-brown or black. They usually occur in persons aged 40 years or older.

Textbooks on genetics, such as those of Snyder [1] and of Gates,[2] do not contain any specific reference to this condition as being congenital. Recent observations on seven families, including those of two local physicians, have impressed me with the belief that Jadassohn's [3] hereditary concept is at present among the more plausible explanations of the origin of seborrheic keratosis.

REPORT OF CASES

Seven families afflicted with seborrheic keratoses are herein reported. Three of these seven families (Figs. 1, 2, and 3) are able to trace the inheritance of the tumors through three generations, and the remaining four families are able to trace it through two generations.

Although seborrheic keratosis as a rule does not occur much before the age of 40, the second- and third-generation members of the second family (Fig. 2) reported that these greasy tumors developed between the ages of 20 and 30. A good record had been kept of the inheritance of these lesions, probably because of the cosmetic disfigurement.

A biopsy specimen was taken from one of the patients mentioned above, a 63-year-old man whose family history is in Figure 2. It revealed a marked epithelial overgrowth and an irregular meshing, primarily of basal epithelial cells. Numerous keratin cyst-like spaces were included in the growth of these cells, and a moderate pleomorphism was present. The tissue changes were characteristic of a seborrheic keratosis.

COMMENT

Seborrheic keratosis and senile keratosis are two different diseases. Caro and Szymanski [4] emphasize the unmistakable clinical, histopathologic, and prognostic differences in these two clinical entities.

1. Snyder, L. T.: Principles of Heredity, Ed. 3, Boston, D. C. Heath & Co., 1946.
2. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, Vols. 1 and 2.
3. Jadassohn, J.: Die benignen Epitheliome, Arch. Dermat. u. Syph. **116**:117-705, 1913.
4. Caro, M. R., and Szymanski, F. J.: Seborrheic and Senile Keratoses, M. Clin. North America **35**:419 (March) 1951.

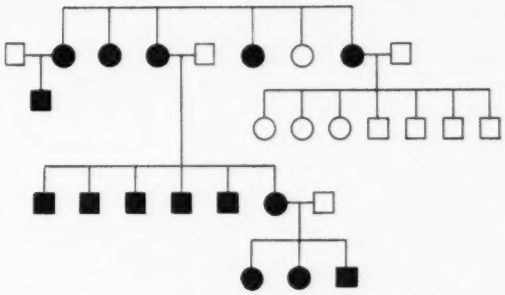

Fig. 1.—Family history illustrating the inheritance of seborrheic keratosis in man traced through three generations. Solid symbols indicate persons affected; hollow symbols, persons unaffected. Squares indicate males; circles, females.

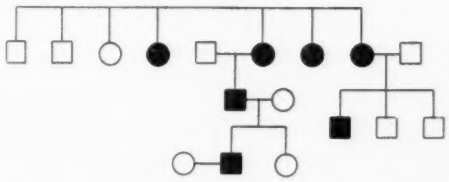

Fig. 2.—Family history illustrating the inheritance of seborrheic keratosis in man traced through three generations. Key to symbols is given in legend to Figure 1.

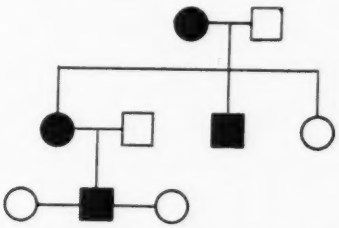

Fig. 3.—Family history illustrating the inheritance of seborrheic keratosis in man traced through three generations. Key to symbols is given in legend to Figure 1.

Fig. 4.—Father, aged 63, with multiple seborrheic keratoses.

At present there is no unanimity of opinion on the exact etiological nature of seborrheic keratosis. Among the numerous and varied opinions concerning its cause are that of Ormsby and Montgomery [5] who considered seborrheic keratosis to be a type of delayed nevus, and that of Pollitzer [6] (the first to give a detailed description of seborrheic keratosis), who reported in histopathologic studies that these keratoses were nevi. In describing Pollitzer's cases, Unna [7] agreed that these keratoses were typical soft nevi with added fat. (The term nevus is used to describe congenital, circumscribed new growths of the skin and does not necessarily mean that the tumor contains nevus cells.) Among the other theories of the cause of seborrheic keratosis are those of Sabouraud,[8] who stated that they were flat papillomas of mediocre development, and of Boyd,[9] who likewise classified them as papillomas. Neumann [10] thought they were the result of changes in aging, senile skin. Lever's [11] concept of seborrheic keratosis as a form of basal-cell epithelioma is somewhat difficult to

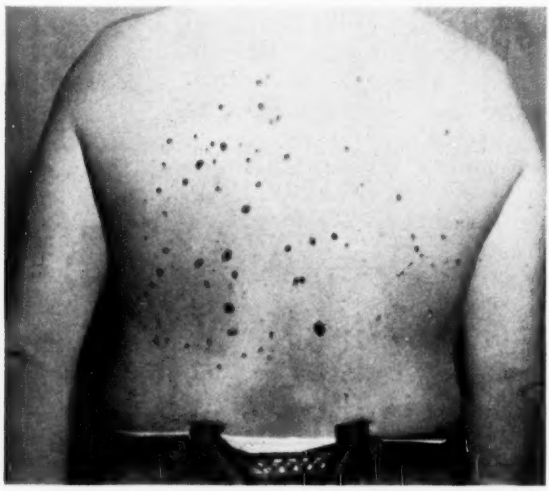

Fig. 5.—Son, aged 37, with multiple seborrheic keratoses.

accept. Becker [12] and Caro and Szymanski [4] believed that these tumors are benign, epidermal neoplasms.

5. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

6. Pollitzer, S.: Die seborrhoeische Warzen, Monatsschr. prakt. Dermat. **11**:145, 1890.

7. Unna, P. G.: The Histopathology of the Diseases of the Skin, translated by N. Walker, New York, The Macmillan Company, 1896.

8. Sabouraud, R. J. A.: Maladies de cuie chevelu: 1. Les maladies seborrheiques, seborrhée, acnes, calvitie, Paris, Masson & Cie, 1902.

9. Boyd, W.: Surgical Pathology, Ed. 6, Philadelphia, W. B. Saunders Company, 1947.

10. Neumann, I.: Über die senilen Veränderungen der Haut des Menschen, Sitzungsb. Akad. Wissensch. Wien **59**:47, 1869.

11. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949, p. 331.

12. Becker, S. W.: Seborrheic Keratoses and Verruca, with Special Reference to the Melanotic Variety, A. M. A. Arch. Dermat. & Syph. **63**:358 (March) 1951.

My genetic report of seborrheic keratosis in members of three generations of th ee families and in members of two generations of four other families, which at nplifies Jadassohn's original report of its occurrence in members of two generations of a family, is of interest because additional information is given about the possible origin of this common condition.

Fig. 6.—Photomicrograph of seborrheic keratosis removed from one of patients.

Presented in 1913 at the International Congress of Medicine in London (Section on Dermatology), Jadassohn's paper *"Die benignen Epitheliome"* included a very interesting discussion on verrucae seniles (seborrheic keratoses). He felt that verrucae seniles, even though resembling verrucae vulgares, were not of an infectious origin. Moreover, earlier attempts on his part to prove an infectious origin had met with no success. He made the point that the lipid content of these lesions was not of importance in giving a clue to the etiological basis. He did feel, however,

that the terrain, or, as Becker [12] has more clearly translated it, the predestination, of the skin must play the main role in the formation of seborrheic keratoses. He told of a family in which the mother and three daughters exhibited seborrheic keratoses between the ages of 20 and 30, and suggested that this condition was probably a familial entity.

While many dermatologists have interpreted the histologic pattern of seborrheic keratosis to be a nevus-like malformation of the skin, the genetic histories given here substantiate Jadassohn's suggestion of the familial nature of these nevus-like tumors.

It is felt that this report on the occurrence of seborrheic keratosis in two and three generations of seven families gives the concept much-needed support. It is of interest to note, also, that there is no record of the development of malignant growths from these tumors in any member of the families.

SUMMARY

Seborrheic keratosis apparently is inherited as a simple dominant trait. Seven family histories are reported in which members of two or three generations have had seborrheic keratosis.

DIETHYLSTILBESTROL THERAPY IN YOUNG MEN WITH ACNE

Correlation with the Urinary 17-Ketosteroids

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AND
C. FERD LEHMANN, M.D.
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THE CURRENT status of acne therapy is aptly recalled by a letter recently received from a sufferer. It is quoted in part:

I am a private in the Army, seventeen years old and suffering with acute acne, I have had it for three years. The doctors seem to pass me as just another case, giving me some ointment and saying if that does not help, we will try something else, with the something else always failing. What I would like to know . . . . is there any sure cure for acne? With all these new drugs, there must be one that will help. I am not speaking only for myself but for hundreds of other guys who have acne also. Please let me know, what I can do.

For many years, acne has been suspected of being related to the androgenic-estrogenic metabolism.[1] Acne is rarely observed in eunuchs. Lawrence and Werthessen[2] have suggested that the specific etiologic factor involved is a disturbed dynamic balance between the two hormones, resulting in insufficient estrogenic potency to protect the person from the acnegenic effect of androgens. Others[3] have recorded themselves as favorable to this concept. Hence it was a natural development that estrogenic substances would be employed therapeutically in acne, since pharmacologically they possess the ability to inhibit many of the androgenic

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Miss Addelia Peterson and Mrs. Jane C. Neff, B.S., of the Fourth Army Area Laboratory, Brooke Army Medical Center, performed the 17-ketosteroid chemical determinations.

From the Dermatology and Syphilology Section, Brooke Army Hospital, Brooke Army Medical Center; Chief of Dermatology and Syphilology (Colonel White); Consultant in Dermatology and Syphilology (Dr. Lehmann).

We acknowledge the cooperation and assistance of Colonel John G. Knauer, Colonel John W. Simpson and Lieutenant Colonel Leo J. Geppert, Medical Corps, United States Army. Colonels Knauer, Simpson, and Geppert are chiefs of Medical, Obstetric and Gynecology, and Pediatric Services, respectively, of Brooke Army Hospital. Lately Colonel Knauer has been reassigned to Valley Forge Army Hospital.

1. Bloch, B.: Metabolism, Endocrine Glands, and Skin Diseases, with Special Reference to Acne Vulgaris and Xanthoma, Brit. J. Dermat. **43**:61, 1931.

2. Lawrence, C. H., and Werthessen, N.: Treatment of Acne with Orally Administered Estrogen, J. Clin. Endocrinol. **11**:636, 1942.

3. Sulzberger, M. B., and Witten, V. H.: Hormones and Acne Vulgaris, M. Clin. North America **35**:373, 1951. Goeckerman, W. H.: Hormonal Therapy in Acne Vulgaris in the Female: A Clinical Attempt At Its Evaluation, Arch. Dermat. & Syph. **61**:237 (Feb.) 1950.

effects.[4] Many physicians prescribe estrogenic medications for acne patients mainly on this basis.

Numerous claims concerning the value of estrogens in acne have been published.[5] Many of these, however, remain unproved.[6] Definite and reliable therapeutic results with estrogens have been obtained in only a few conditions.[4] Ormsby and Montgomery[7] have written that apparently estrogens have not been of the value they promised to be when first introduced in acne therapy. Sutton[8] thinks it fair to say that therapeutic results with hormonal substances have been irregular, unsatisfactory, and unpredictable. Yet, estrogenic substances are widely used today by competent dermatologists[9] as adjunctive treatment in acne. Andrews,[10] although relying more heavily on the antibiotics and decrying the use of estrogenic substances as the sole treatment of acne, apparently in a fairly routine fashion employs diethylstilbestrol in small dosages over prolonged periods.

In the military, the ever-current problem of acne is a serious cause of ineffectiveness and morbidity, and it accounts for approximately 10% of the dermatologic admissions to this hospital and clinic. The local management is time-consuming and laborious, for both the patient and the doctor. In our hands, therapeutic results leave much to be desired and have been far from ideal. Consequently, more specific and direct agents of therapy are constantly being pursued. Because of the large numbers of hopeful patients seeking a cure, the opportunity is ample for detailed, daily, clinical studies and laboratory procedures not generally obtainable in civilian practice. Although awed by the enormity of this problem but aware of its complexities and fallacies, we have attempted to evaluate the usefulness of diethylstilbestrol as an adjuvant in the treatment of acne.

Extensive urinary 17-ketosteroid assays were undertaken in an effort to uncover a laboratory measurement for the evaluation of estrogenic effects in acne. Such a measurement would prove useful in clarifying the acne problem and would help to avoid many of the pitfalls inherent in clinical, interpretative analyses, even when rendered by sound investigators.[11] We are indebted to B. Bloch[1] for this admonition:

> It is absolutely wrong to think that the almost endlessly repeated determination of any arbitrarily selected chemical component of the blood, the intestinal contents, the urine, in all sorts of skin-diseases must inevitably provide an insight into the metabolism itself or into the metabolic causes of the skin-diseases.

4. Diethylstilbestrol, Action, and Uses, in New and Nonofficial Remedies, Council of Pharmacy and Chemistry, American Medical Association, 1950, Philadelphia, J. B. Lippincott Company, 1950, p. 331.

5. Way, S. C., and Andrews, G. C.: Hormones and Acne, Arch. Dermat. & Syph. **61**:575 (April) 1950.

6. Cohen, E. L.: Endocrine Factors in Acne Vulgaris, Brit. J. Dermat. **53**:231, 1941.

7. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 1321.

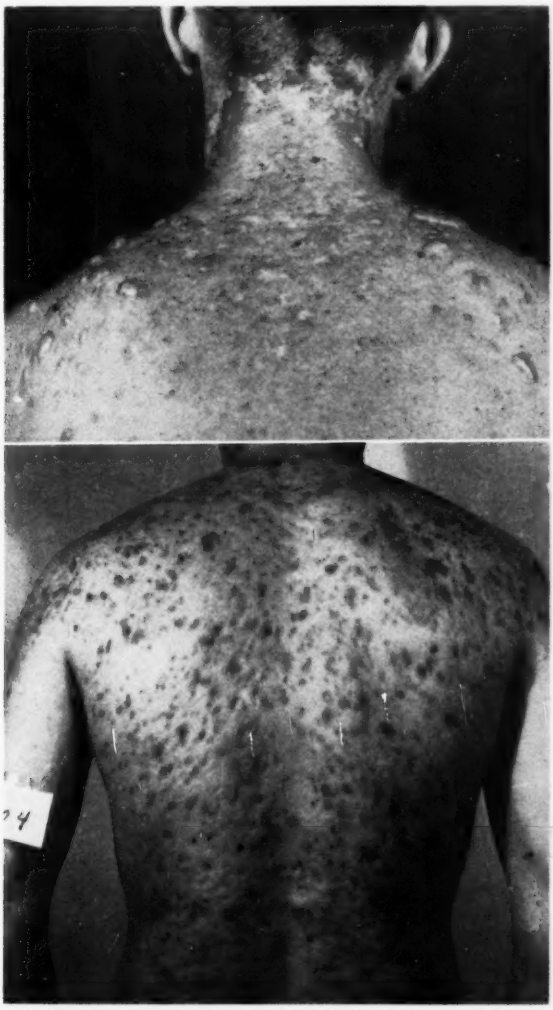
8. Sutton, R. L.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949, p. 406.

9. Sulzberger, M. B., and Baer, R. L.: Acne Vulgaris and Its Management, in The 1949 Year Book of Dermatology and Syphilis, Chicago, The Year Book Publishers, Inc., 1949, p. 9.

10. Andrews, G. C.: Domonkos, A. N., and Post, C. F.: Modern Treatment of Acne Vulgaris, J. A. M. A. **146**:1107 (July 21) 1951.

11. Estrogens and Androgens in Mammary Cancer, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **140**:1214 (Aug. 13) 1949.

Still (with due respect to Bloch) we embarked upon an arduous if brazen attempt to correlate the urinary 17-ketosteroid excretion with diethylstilbestrol therapy in the acne patient. The rationale for the use of the urinary 17-ketosteroid assay in acne has been previously recounted.[12]



Samples of acne classified as severe in degree.

MATERIAL

The clinical material comprising this study totaled 97 cases and was selected from two separate sources. Of these cases 26 were in patients on the hospital ward; 71 were in outpatients treated in the dermatology clinic. All patients were youths and men in the military service

12. White, C. B.; Peterson, A., and Neff, J. C.: Acne Vulgaris and the Urinary 17-Ketosteroids in Young Men, to be published.

between the ages of 15 and 30. The majority were in the age group between 18 and 24. Practically all the clinical varieties of acne were represented and were classified as severe or moderately severe in degree. The acne was slightly more severe in the hospital series. In the majority the condition was of over one year's duration.

The 26 hospital patients had been transferred from distant locales because of their general intractability. The 71 clinic patients were derived from military personnel and dependents assigned to adjacent military establishments. These 71 patients were selected from a group of 492 acne patients by the following criteria: sex, male; age, between 17 and 25; degree of acne, either severe or moderately severe, and period of observation, at least three months. Although girls and women comprised 35% of the 492, we excluded them from the study because we desired a series of outpatients comparable to the series of hospital patients who were all male. Also it was striking that the degree of acne involvement in these girls and women was notably less severe than in the youths and men. A continuous effort was made to exclude, as far as possible, the extraneous variables which are inherent in studies of this type.

METHOD AND PROCEDURE

The study began in January, 1949, and is divided into two distinct phases which were extended over a period of two and one-half years. The first phase deals with hospital-ward patients exclusively, and it is separated into two series: one diethylstilbestrol-treated, 14 patients (Stilbestrol 1), and one nondiethylstilbestrol-treated, 12 patients (Control A). The second phase of the study deals with outpatients exclusively and is separated into two series: one diethylstilbestrol-treated, 21 patients (Stilbestrol 2), and one nondiethylstilbestrol, 50 patients (Control B).

Hospital Series.—Between January and August, 1949, all acne patients classified as severe or moderately severe in degree, admitted to the hospital ward, were treated with a comparable base-line therapeutic regimen. This included bed rest, careful personal hygiene, daily cleansing, dietary limitations of fats, sweets, nuts, iodides, and chocolates, acne surgery, and orthodox local remedies, such as white lotion, scalp lotions, and sulfurated lime solution. Antibiotics, mainly penicillin and sulfadiazine, were employed freely whenever indicated.

Twenty-four-hour urine specimens, for 17-ketosteroid determinations, were collected upon admission and thereafter at weekly intervals until this phase of the study was finished in August, 1949. At the end of the second week of hospitalization, after each patient's base-line response to hospital routines and environment was ascertained, diethylstilbestrol-therapy studies were begun, alternate patients being used. These alternate patients were selected merely on the basis of chronologic order of admission, without reference to the severity of the acne process. Diethylstilbestrol was administered in a minimal dosage of 40 mg. daily for 20 days and a maximal dosage of 154 mg. for 77 days. The average dosage was 88 mg. for 50 days. The companion control patients were given adjunctive placebo therapy consisting of sodium bicarbonate pills in lieu of diethylstilbestrol. In two patients with very severe acne, who initially had been in the sodium bicarbonate series, diethylstilbestrol was later administered, but only after both patients had completed a two-month period as controls.

During the initial phase of the study, all dosage records were maintained solely by the ward nurse and were unknown to the ward doctors. One question which we attempted to answer was whether unbiased dermatologists [13] could determine correctly the identity of the patients who were receiving diethylstilbestrol, purely on the grounds of distinctive clinical improvement alone. The appearance of gynecomastia was observed and became helpful in assaying the biologic activity of the estrogen received.

The technicians who performed the 17-ketosteroid chemical determinations at the time were unaware of the scope or exact content of this study. Usually eight to twelve 24-hour urine specimens were titrated at weekly intervals, and the technicians did not know the series identity of the various specimens.

13. Dr. Thomas H. Diseker, Dr. J. Lewis Pipkin, and Dr. Duncan O. Poth, Consultants in Dermatology, Brooke Army Hospital, and Major John J. Pope, Lieutenant Colonel Van R. Richmond, and Lieutenant Colonel Urban L. Throm, Residents in Dermatology and Syphilology, assisted in this phase of the study.

Clinic Series.—The cases of these 71 patients were basically comparable to the hospital series. Fifty of these outpatients served as Control B. They were seen at one- or two-week intervals. Basic therapeutic methods, as in the hospital series, were employed, except for two important differences. Whereas the hospital patients were treated daily on the ward, the clinic patients were given prescriptions and were instructed concerning self-medication. Moreover, acne surgery was not as regularly performed. Hence, except in rare instances, clinic patients did not receive as good local care as the hospital patients.

The 21 diethylstilbestrol-treated patients were selected essentially in the order in which they presented themselves as patients in the dermatology clinic between October and December, 1950. These patients were managed similarly to those in the hospital series, and the diethylstilbestrol dosage was comparable. No ketosteroid assays were performed in these cases.

TABLE 1.—*Urinary 17-Ketosteroid Excretions in Young Men with Acne Vulgaris* *

Patient	Age, Yr.	Degree of Acne	Duration of Study, Days	No. Tests 17-Ketosteroids †	17-Ketosteroid Range, Mg./24 Hr.		17-Ketosteroid Average Excretion, Mg./24 Hr.
					Low	High	
B. L.	15	Severe	49	6	9.5	18.2	12.9
M. D.	17	Moderate	70	6	10.6	21.9	15.5
P. F.	18	Severe	231	12	3.7	11.9	7.6
T. G.	18	Moderate	84	11	3.8	12.9	9.0
R. M.	18	Moderate	133	12	4.3	20.3	10.3
W. H.	18	Severe	140	3	8.6	13.7	11.2
P. C.	18	Severe	126	3	11.9	13.8	12.9
L. B.	19	Moderate	77	3	4.8	7.4	5.8
E. A.	19	Moderate	98	2	9.1	10.5	9.8
A. A.	19	Moderate	56	2	12.9	14.9	13.9
D. S.	19	Severe	161	11	10.9	20.1	14.1
N. B.	20	Moderate	70	7	10.0	19.3	13.9
C. B.	20	Moderate	14	1	14.3	14.3	14.3
T. H.	20	Severe	91	6	10.3	21.4	14.5
D. W.	20	Moderate	42	6	9.6	20.1	15.3
R. H.	20	Severe	77	2	15.8	18.3	17.0
P. K.	20	Moderate	161	11	2.7	27.1	18.6
S. L.	20	Severe	91	3	17.0	24.8	21.8
C. N.	21	Severe	49	5	5.0	12.9	8.4
R. P.	21	Severe	84	3	8.9	10.7	9.6
J. T.	22	Severe	63	6	12.9	22.9	18.7
P. H.	22	Moderate	119	3	16.6	22.1	19.7
W. S.	23	Moderate	28	3	12.9	15.6	14.3
C. H.	24	Severe	133	2	13.6	23.7	18.6
W. C.	24	Moderate	42	4	18.9	24.0	20.3
F. R.	30	Moderate	35	3	8.6	11.9	10.2
Averages	20		80	5.2	10.3	17.5	13.8

* Hospital group: 26 patients, 136 determinations.
† Majority of 17-ketosteroid tests were performed at weekly intervals.

RESULTS

Hospital Series.—The group-control data on the 17-ketosteroids obtained in this experiment are shown in Table 1. These data have formed the basis of a separate report.[12] The average daily excretion of the urinary 17-ketosteroids for a group of 26 young men with acne, between the ages of 15 and 30, was found to be 13.8 mg. per 24 hours. This value falls well within the normal range for healthy young men of similar age. In the entire study a total of two hundred and twenty-eight 17-ketosteroid chemical determinations were titrated.

A uniform and consistent decrease in the values for the urinary 17-ketosteroids was found to occur concomitantly with diethylstilbestrol medication. This finding

has been reported by others [14] in various conditions. During the course of diethylstilbestrol administration, the average 17-ketosteroid output was 4.4 mg. lower than that in the average group control and 4.2 mg. lower than that in the average pretreatment individual control. However, this suppressive effect of diethylstilbestrol could not be correlated with distinctive clinical improvement in the acne lesions in any specific case. We had become intrigued by the observations of one author [15] that estrogenic therapy in acne, in sufficient dosage, causes comedones to shrivel and become desiccated. We could not substantiate this observation by the results observed in any of our patients, with the dosage employed. On the contrary, competent observers were rarely able to distinguish by visual inspection

TABLE 2.—*Incidence of Gynecomastia and Temporary Suppression of 17-Ketosteroid Excretion in Fourteen Young Men with Acne Vulgaris Treated with Diethylstilbestrol* *

	Diethylstilbestrol Therapy						
		During					After †
Patient	Before Average 17-Ketosteroid Excretion, Mg./24 Hr.	Duration Therapy, Days	Total Dosage, Mg.	Average 17-Ketosteroid Excretion, Mg./24 Hr.	Suppression 17-Ketosteroid Output, Mg./24 Hr.	Gynecomastia	Average 17-Ketosteroid Excretion, Mg./24 Hr.
P. F.	7.6	62	124	6.5	1.1	+	...
W. H.	11.2	60	93	6.9	4.3	++	8.4
D. S.	14.1	20	40	11.8	2.3	0	...
P. K.	18.6	20	40	16.0	2.6	+	16.4
P. C.	12.9	60	93	7.1	5.8	+	...
R. P.	9.6	60	93	6.3	3.3	0	...
P. H.	19.7	60	93	10.8	8.9	0	21.2
L. B.	5.8	56	102	4.0	1.8	0	...
C. H.	18.6	77	154	16.4	2.2	++	24.1
R. H.	17.0	60	120	10.9	6.1	++	13.0
E. A.	9.8	56	112	4.0	5.8	++	...
S. L.	21.8	21	42	13.8	8.0	0	...
A. A.	13.9	42	84	7.0	6.9	+	
R. M.	10.3	30	60	9.3	1.0	+	...
Average	13.6	50	88	9.4	4.2	64%	16.6

* Hospital series: 164 ketosteroid determinations.
† One to two months after cessation.

the diethylstilbestrol-treated patients from the placebo controls. There appeared to be very little differences between the two series (Stilbestrol 1 and Control A). In both series, the change noted was toward a slow but undramatic improvement. When two patients with very severe acne who were initially managed as controls were later given diethylstilbestrol because of a poor initial response, no impressive improvement was obtained. No distinctive patterns of effect in the diethylstilbestrol-treated patients were detected as regards either the degree or the rate of satisfactory response.

14. Hamblen, E. C.; Pattee, C. J., and Cuyler, W. K.: Alterations of Urinary Excretion of Androgen by Estrogenic Therapy, Endocrinology **27**:734, 1940. Deakins, M. L.; Friedgood, H. B., and Ferrebee, J. W.: J. Clin. Endocrinol. **4**:376, 1944; cited by Masow, H. L., and Engstrom, W. W.: The 17-Ketosteroids, Their Origin, Determination and Significance, Physiol. Rev. **30**:321, 1950.

15. Barber, H. W.: The Influence of Sex Hormones, in MacKenna, R. M. B.: Modern Trends in Dermatology, London, Paul B. Hoeber, 1948, p. 115.

Other metabolic effects of diethylstilbestrol medication were easily detected. These included mammary-gland enlargement, nausea, anorexia, slight loss of weight, diminution of libido, and other evidences of mild feminization. These patients became docile, passive, and easier to manage on the ward. However, all side-effects appeared to be temporary and promptly disappeared upon withdrawal of diethylstilbestrol.

In the clinic series, the 21 patients (Stilbestrol 2) did no better and no worse than the 50 patients treated without diethylstilbestrol (Control B). However, in all 71 patients the clinical response was generally less satisfactory than results obtained among patients treated in the hospital series. Estrogenic side-effects were similar to those previously described.

Two of the patients in this series of 21 were treated solely with diethylstilbestrol, in dosage of 2 mg. daily for 30 days. In both, the acne process became worse. At the end of the one-month period, a satisfactory response was obtained when the use of diethylstilbestrol was discontinued and energetic local measures were applied.

TABLE 3.—*Clinical Response of Ninety-Seven Patients With and Without Adjunctive Diethylstilbestrol Therapy*

Series	No. of Cases	Clinical Response			
		Satisfactory *		Poor †	
		No.	Per Cent	No.	Per Cent
Hospital					
Stilbestrol 1	14	9	64	5	36
Control A	12	8	66	4	34
Clinic					
Stilbestrol 2	21	11	52	10	48
Control B	50	27	55	23	45

* Acne lesions became inactive or tractable.
† New acne lesions appeared and continued active although abated.

COMMENT

This study is too small and limited in scope to allow definite conclusions. It was undertaken as a pilot study, which, had it proved sufficiently promising, could easily have been enlarged and extended. However, the failure to obtain more definite or profitable therapeutic results in these few, together with a basic uncertainty as to the systemic harmlessness of estrogenic therapy, discouraged the more-widespread use of diethylstilbestrol in acne patients at this time.

Although we suspect that massive dosage schedules (10 to 15 mg. daily) of estrogenic substances, similar to those used in advanced cancer of the breast,[16] would be effective in controlling acne lesions, discreet medical judgment precludes such usage. Nathanson recently has called attention to the potentiality of serious complications associated with massive doses and warns that extreme caution must be exercised during the entire treatment period. It appears probable that, with the present hormonal substances available, no dosage schedules short of those approaching the pituitary-suppression level will adequately control acne, even temporarily.

16. Nathanson, I. T.: Hormones and Castration in Advanced Breast Cancer, Radiology **56**:535, 1951.

Until such time as estrogenic-like compounds with more specific action and with fewer undesirable side-effects become available, the hormonal treatment of acne will probably remain unsatisfactory.

We have only a very limited experience with the minimal-dose (0.25 mg. daily), long-term technique of diethylstilbestrol therapy. Our results have not been encouraging.

SUMMARY

In 14 acne patients, diethylstilbestrol therapy, given in dosage of 1 to 2 mg. daily for 20 to 77 days, caused a significant suppression of the urinary 17-ketosteroid excretion. Such management likewise caused a definite gynecomastia in 9 of 14 patients after a period of three to four weeks of estrogen therapy. Other estrogenic effects included nausea, anorexia, diminution in libido, and slight evidences of feminization. These estrogen effects promptly disappeared in two to three weeks after withdrawal of the diethylstilbestrol.

Distinctive clinical improvement in acne lesions did not accompany either the estrogenic effects or the 17-ketosteroid suppression. Clinical improvement in 14 diethylstilbestrol-treated patients was indistinguishable from the improvement observed in 12 nondiethylstilbestrol-treated patients, managed in chronologic parallel in the hospital. No significant difference in either degree or rate of improvement was noted in 21 clinic patients as a result of diethylstilbestrol therapy when compared with the improvement noted in 50 control patients from the same clinic. Better therapeutic results were observed in 26 acne patients managed in the hospital ward than in 71 managed as outpatients. These better results we attribute to the superiority of local measures applied in the hospital. In short, 62 acne patients managed by orthodox measures, without diethylstilbestrol, accomplished clinical improvement similar in degree and rate to that attained by 35 patients treated adjunctively, with diethylstilbestrol.

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Clinical Notes, New Instruments and Techniques

THE DERMATOLOGIST AND THE CORNELL MEDICAL INDEX-HEALTH QUESTIONNAIRE

SAMUEL D. ALLISON, M.D.
HONOLULU, T. H.

Help is at hand for the dermatologist who is confused as to the best method of obtaining significant medical and psychiatric data quickly and weighing the relative importance of these data.

Early last year there was introduced to the profession-at-large the Cornell Medical Index-Health Questionnaire.[1] This was described as "a self administered instrument that collects a large body of significant medical and psychiatric data without the physician's participation...." The 195 questions are answerable by "yes" or "no," can be answered by the patient in 15 to 20 minutes, and provide "a background of information about the patient's total medical problem, to aid in interpretation of the manifestations of disease in the specialty...."

This questionnaire is a useful adjunct to the dermatologist in the management of a variety of cases and has been found particularly useful in evaluating and interpreting the relative weight of medical and psychiatric aspects of eczema.

There is an increasing awareness of the role which emotions play in skin disorders. And even though a sizable number of papers[2] have appeared concerning the psychiatric aspect of dermatology, some of us are still baffled as to how to assay their relation to the skin, how to interpret them to the patient, and how, ultimately, to manage the emotional components of the disorder—whether to attempt to manage them ourselves or whether to insist upon psychiatric aid. The Cornell form is a great aid in this problem.

Some of the completed questionnaires reveal a paucity of psychiatric leads, others suggest an emotionally tinged illness, while a few present the whole gamut of symptoms listed recently by Purtell as those characteristic of hysteria.[3] Some will suggest ease of management and quick alleviation of presenting symptoms; others will portend failure—or at the most, mitigation of dermatologic distress but not removal of the basic pathology. For example, a 27-year-old office worker who had suffered from recurrent mild attacks of neurodermatitis for 12 years was found by the questionnaire to have many symptoms related to organs other than the skin and a large number of complaints related specifically to the emotions. Among symptoms probably caused exclusively by her emotions were "choking lumps in the throat," gulping of food, bad constipation, headaches, nocturia, complete exhaustion (which on further questioning was found to be related to her job and not to her week-end activities), and insomnia. The Cornell form presents 40 questions specifically related to the emotions. This young woman answered "yes" to 19 symptoms, such as difficulty in making up her mind, feeling of unhappiness and depression, worrying, shyness, feelings easily hurt, etc. The patient was annoyed at a previous physician who had attributed her condition to "nerves." After answering the Cornell questionnaire it was apparent to the patient, as it was to the physician, that her skin problems were similar to her many other problems and that most of them were on an emotional basis. In her case, as in many others, the use of this form has materially aided in elucidating and interpreting the emotional aspects of a dermatologic disorder.

1. Brodman, K.; Erdmann, A. J., Jr.; Lorge, I., and Wolff, H. G.: The Cornell Medical Index-Health Questionnaire, J. A. M. A. **145**:152 (Jan. 20) 1951.

2. Williams, D. H.: Management of Atopic Dermatitis in Children: Control of the Maternal Rejection Factor, A. M. A. Arch. Dermat. & Syph. **63**:545 (May) 1951. English, O. S.: Role of Emotion in Disorders of the Skin, ibid. **60**:1063 (Dec.) 1949. Wright, C. S.: Therapy of Psychosomatic Dermatoses, ibid. **60**:303 (Aug.) 1949. Gottesman, A. H., and Menninger, K.: The Dermatologist and the Psychiatrist, ibid. **59**:367 (April) 1949.

3. Purtell, J. J.; Robins, E., and Cohen, M. E.: Observations on Clinical Aspects of Hysteria, J. A. M. A. **146**:902 (July 7) 1951.

It is believed that by the judicious use of the Cornell Medical Index we dermatologists can be better informed about the medical and psychiatric aspects of skin disorders. Our horizon will be wider. We shall be aided in assaying the relative role played by the emotions, we shall be better able to interpret to the patient the underlying causes of many conditions, and we shall be aided in our referral for additional psychiatric or medical help. The use of the Cornell form, or a dermatologically oriented equivalent, should enhance our ability to understand and treat a variety of skin conditions.

342 Young Hotel Bldg. (13)

FUNGICIDAL ACTIVITY IN VITRO OF PODOPHYLLOTOXIN

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Young [1] reported recently that a 3.3% solution of podophyllotoxin in 90% alcohol had a marked fungicidal action upon hairs infected with Microsporum audouini. No growth was obtained after immersion of infected hairs for as little as one minute. He also reported 64% of cures after treatment of tinea capitis for six weeks with the concentration of podophyllotoxin mentioned above.

I obtained podophyllotoxin from the same source [2] as Young and prepared a 3.3% solution in 90% alcohol. I could not confirm its fungicidal activity in vitro. I obtained growth of M. audouini after immersing infected hairs not only for 1 minute but even for 15 minutes, one hour, and three hours. The procedure I followed was to place the infected hairs in the solution for the stated interval, rinse them with alcohol several times, and then transfer them to Sabouraud's culture medium. It is possible that Young may not have rinsed the infected hairs after immersion in the podophyllotoxin solution, and so have left a layer of the toxin on the hair to act as a physical barrier to growth on the culture medium.

In view of the fact that podophyllotoxin is not an effective fungicide in vitro for hairs infected with M. audouini, I must conclude that the favorable results reported by Young in the treatment of tinea capitis must be due to factors other than its fungicidal action.

SUMMARY

A 3.3% alcoholic solution of podophyllotoxin is not an effective fungicide for hairs infected with Microsporum audouini, when tested in vitro.

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1. Young, C. J.: Podophyllotoxin Treatment of Microsporon Audouini Scalp Infections, A. M. A. Arch. Dermat. & Syph. **64**:607 (Nov.) 1951.

2. The podophyllotoxin was furnished by S. B. Penick & Company, New York.

PAPULAR NECROTIC TUBERCULID DEVELOPING DURING CALCIFEROL THERAPY

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The occurrence of a tuberculid during treatment of cutaneous tuberculosis with calciferol is uncommon. Green,[1] at the Royal Society of Medicine, showed a case of a woman with lupus vulgaris of the face in whom, during treatment with calciferol, a papular tuberculid of the face developed. Fletcher,[2] at the Annual Meeting of the Dermatological Society of Great

Consultant dermatologist, Gateshead and South Shields Area, County Durham, England.

1. Green, B.: Proc. Roy. Soc. Med. **40**:253, 1946.

2. Fletcher, D.: Unpublished data, 1949.

Britain in 1949, showed a case of a patient with lupus vulgaris involving the face in whom a tuberculid developed during calciferol treatment.

The case presented here is that of a woman, aged 53, who came to the hospital for treatment of ulcerating lupus vulgaris involving the skin of the elbow region.

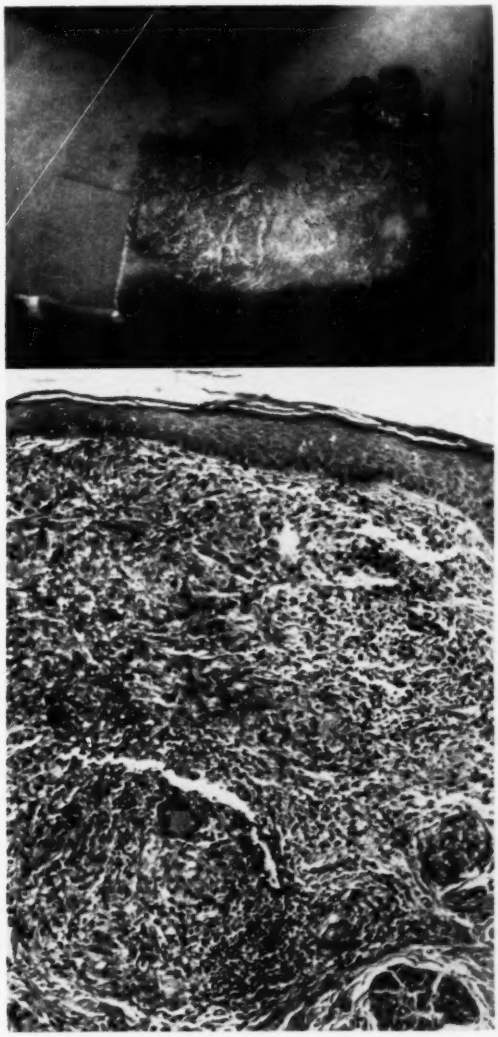

Fig. 1.—Upper, lupus vulgaris affecting left elbow region. Lower, section of skin from same lesion.

She gave a history of an operation in childhood upon the bones of the left elbow. After this the skin lesion had appeared and had gradually enlarged. During the winter the affected area was moist and ulcerated, but in summer it tended to dry up.

When seen in the hospital she presented an extensive area of lupus vulgaris affecting the left elbow region advancing to encircle the arm over the cubital fossa (Fig. 1, upper). Parts of

the lesion were moist and ulcerated. A roentgenogram of the elbow revealed no signs of past bone infection, and histological examination of a portion of the skin confirmed the diagnosis of lupus vulgaris (Fig. 1, lower).

Treatment with calciferol, 50,000 units daily, was begun, and after two weeks the dose was increased to 100,000 units daily. During the sixth week of treatment a profuse reddish-brown papular rash appeared on the calves and ankles (Fig. 2, upper). The papules were indurated, and some were undergoing necrosis. The skin of the crural regions was bluish-red and cool on

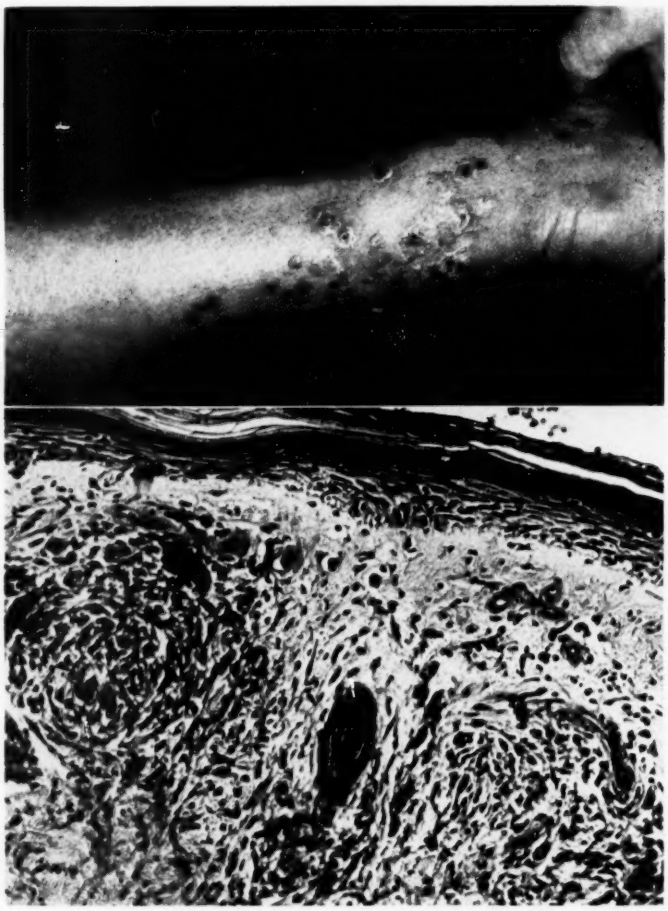

Fig. 2.—Upper, papular rash on ankle following calciferol therapy. Lower, section of papule, same lesion, showing tuberculid character of lesion.

palpation; there were numerous spidery venules, and the circulation was sluggish. There were no subjective toxic symptoms from the calciferol.

A histological examination of one of the papules showed the lesion to be a tuberculid (Fig. 2, lower). The erythrocyte sedimentation rate was 4 mm. in one hour (Westergren). The leucocyte count was 6,400 cells per cubic millimeter, with 63% neutrophils, 32% lymphocytes, 4% monocytes, and 1% basophils. A roentgenogram of the lungs showed a calcified primary complex in the left apical region.

The treatment was continued at a dosage of 50,000 units daily for another three weeks; fresh papules were appearing during this period, and the patient complained occasionally of thirst and slight nausea. A tuberculin patch test with control was performed on the forearm, using "tuberculin diagnostic jelly" (Allen & Hanburys, London) containing 60% volume by weight old tuberculin. Within 48 hours there was a severe reaction; the test area showed a group of reddish-brown papules, some of which proceeded to necrosis. They persisted for many weeks.

For a further six weeks the treatment with 50,000 units of calciferol was continued, and during this time there were no complaints of thirst or nausea. The papules were still appearing on the legs, and many had proceeded to necrosis and scarring. The lesion at the elbow was showing areas of pale scarring which were free from "apple-jelly" nodules, but the appearance of the legs was alarming the patient. At this stage the use of calciferol was discontinued after a total of 14 weeks' treatment. For two months after this fresh papules continued to appear on the legs. When seen four months after cessation of treatment, the tuberculid had healed leaving numerous white scars. The elbow showed healed areas, but there were many active nodules at the periphery. Another tuberculin test was performed using the same diagnostic jelly, and after 48 hours there were a few slightly raised papules which faded in one week. The patient was unwilling to have further treatment with calciferol.

COMMENT

Considering the large number of patients with lupus vulgaris who have been treated with calciferol, it is surprising that such development of a tuberculid as described here has not been seen oftener. It would seem in this case that, during its action of healing, the calciferol released substances from the lupus area which found their way to the areas of venous stasis in the lower limbs. Sluggish circulation may have caused a prolongation of their effect upon the skin which at that time was vigorously hypersensitive to tuberculin. Unfortunately, no tuberculin test was performed before treatment with calciferol was instituted. However, some time after cessation of treatment and healing of the tuberculid, the skin sensitivity to tuberculin was less. So it may be presumed that the hypersensitivity was connected with the action of calciferol in healing the lupus vulgaris.

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TERRAMYCIN THERAPY OF MOLLUSCUM CONTAGIOSUM

COLEMAN MOPPER, M.D.
DETROIT

As a result of experimental work by Juliusberg [1] and Wile and Kingery,[2] molluscum contagiosum has been considered for many years to be caused by a filtrable virus. Prior to the advent of chemotherapy, treatment had consisted of local destruction of individual lesions by curettage or escharotics. Within the past 10 years several chemotherapeutic agents have been used, including sulfapyridine,[3] sulfathiazole,[4] and recently aureomycin.[5] All of these, however, have

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1. Juliusberg, M.: Zur Kenntnis des Virus des Molluscum contagiosum des Menschen, Deutsche med. Wchnschr. **31**:1598-1599, 1905.

2. Kingery, L. B.: Histogenesis of Molluscum Contagiosum, Arch. Dermat. & Syph. **2**:144 (Aug.) 1920.

3. Hill, W. R., and Downing, J. G.: Molluscum Contagiosum Cured with Sulfapyridine, Arch. Dermat. & Syph. **46**:139-140 (July) 1942.

4. Laymon, C. W.: Molluscum Contagiosum Treated with Sulfadiazine, Arch. Dermat. & Syph. **53**:643 (June) 1946.

5. Guy, W. H.; Jacob, F. M., and Guy, W. B.: Aureomycin in Molluscum Contagiosum, Arch. Dermat. & Syph. **60**:629 (Oct.) 1949.

been of limited or no value in many cases, and there have been recent reports of failures with aureomycin.[6] With this in mind, another antibiotic was used.

B. D. a 2-year-old Negro girl, was seen on July 24, 1951. She presented about 25 to 30 typical lesions of molluscum contagiosum. One lesion was noticed several months ago, and new ones have continued to appear. Because of the extreme difficulty of curetting these lesions in an active child, it was decided to use an antibiotic in liquid form to facilitate its ingestion. An elixir of terramycin, 1 teaspoonful four times daily for four days, was prescribed. The patient was seen one week later, and at that time about one-half of the lesions had involuted, and the remaining ones were much smaller. The terramycin dosage was repeated for four more days, and when the patient was seen the following week all the lesions had disappeared completely.

It was deemed advisable to report the excellent response of molluscum contagiosum to terramycin in this case, so that other dermatologists might use this convenient form of therapy. Only with use of this drug in a number of cases will its true value be established. I am aware of spontaneous cures, and a number of reports will have to be made and studied to determine the effectiveness of terramycin in molluscum contagiosum.

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6. Feiler, Harry B.: Molluscum Contagiosum, Treated with Aureomycin, A.M.A. Arch. Dermat. & Syph. **64**:246 (Aug.) 1951.

ERYTHRASMA FLUORESCENCE UNDER THE WOOD LIGHT

PARASKEVAS MICHAELIDES, M.D.
AND
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Several years ago we accidentally observed a bright-red fluorescence of a lesion of the genitocrural area under the Wood light. The lesion was a dry, reddish-brown plaque with sharply demarcated borders, no papules or vesicles, and slight, powdery scaling. Clinically, the lesion was typically that of erythrasma, and microscopic examination of the skin scrapings under oil immersion showed short, delicate, branching filaments and small coccoid forms characteristic of Nocardia minutissima, the causative agent of erythrasma. Repeated examinations over a period of a month, with care taken to avoid any local applications so as to obviate the possibility of fluorescence due to foreign substances such as medicaments, did not show any change in the appearance of the fluorescence.

We have since used the Wood light on all lesions of the genitocrural and axillary areas resembling erythrasma or tinea cruris. No lesion of tinea cruris, proved by microscopic examination, or of seborrheic dermatitis of these areas has shown any characteristic fluorescence. A characteristic bright-red fluorescence has been seen only in the lesions of erythrasma but not in all of these. The red fluorescence, when present, may correspond to the entire erythrasma lesion, may form a border at the edge of the lesion, or may form patches within the lesion. In each case the fluorescence appears only within the limits of the erythrasma lesion, but does not necessarily occupy the whole of the lesion. Wherever there is fluorescence, one can find the organism by microscopic examination. We have observed some cases of erythrasma, proved by microscopic examination, with no fluorescence whatsoever.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

This bright-red fluorescence is not specific for erythrasma, for various shades of red fluorescence are seen in sebaceous secretions, dental tartar and gingival deposits, lingual mucosa, and ulcerated squamous-cell epitheliomas.

To sum up, the bright-red fluorescence is not always present and does not necessarily cover the entire clinical lesion of erythrasma. Red fluorescence can be seen elsewhere than in the erythrasma lesion. However, we have seen no other dermatoses with the topographic distribution in axillae and genitocrural area producing the fluorescence seen in erythrasma lesions.

We have found no special mention of the fluorescence of erythrasma lesions in the standard dermatologic textbooks. The papers on erythrasma and on the use of the Wood light in the American periodicals have likewise not emphasized this fluorescence. However, in an article in the French literature by Gougerot and Duché,[1] this same bright-red fluorescence of the erythrasma lesion is pointed out and discussed. Our observations parallel those of Gougerot.

CONCLUSIONS

The use of the Wood light on axillary and genitocrural lesions may provide a rapid method of diagnosing erythrasma.

The presence of the characteristic, bright-red fluorescence has always been indicative of erythrasma in our series of cases.

The absence of the fluorescence does not exclude the diagnosis of erythrasma.

1. Gougerot, H., and Duché, J.: Les trois teintes brune, brun violacé, rouge de l'erythrasma à la lumière de Wood, Ann. dermat. et syph. **1**:277, 1941.

VESICULAR LESIONS IN SECONDARY SYPHILIS

Report of a Case

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AND
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CINCINNATI

There is an axiom that vesicular lesions in an adult are never due to secondary syphilis. Howles,[1] however, has indicated that he has seen a number of cases in Negroes. As a further exception to that rule, the following case in a young white woman is reported.

REPORT OF CASE

J. R., a 21-year-old white prostitute, was sent to the Cincinnati Workhouse Quarantine Hospital, where she was found to have a positive reaction of 160 Kahn units to the serological test for syphilis. On repetition two days later, the serological test for syphilis gave a positive reaction of 360 Kahn units. At the time of her admission there, she stated that for the past three weeks she had had blisters on her palms, which, when pricked, yielded a clear fluid. Examination of the fluid under the dark-field microscope showed it to contain numerous Treponema pallidum organisms.

There was no history of previous illness. The patient took no drugs or patent medicines and came in contact with no known irritants. There was no suggestion of allergic tendency. Serological tests for syphilis made in 1946, 1947, and 1949 all yielded negative results, and she denied any previous episodes of venereal disease.

From the Department of Dermatology and Syphilology (Leon Goldman, M.D., Director), University of Cincinnati College of Medicine.

1. Howles, J.: Personal communication to the authors.

The patient was referred to the Cincinnati General Hospital for therapy. On her admission there, physical examination revealed a young white woman who appeared to be in good general health. Abnormal findings were limited to the palmar vesicles. On both palms (Figure) were copper-colored papulovesicular lesions 6 to 8 mm. in diameter in a somewhat circinate arrangement. A few scattered vesicles were present on the volar surfaces of the fingers. Clear fluid could be obtained by rupture of the vesicles. No lesions of any sort were present on the feet.

The patient's hospital and clinic course was in accordance with the therapeutic procedure then under evaluation. She was treated with 2,700,000 units of penicillin procaine in oil over a period of nine days. No Herxheimer reaction occurred. By the third day of therapy the

Vesicular lesions of the palms in secondary syphilis.

vesicles had become pale and shrunken. On her discharge from the hospital they were almost gone.

One month later a serological test for syphilis showed 20 Kahn units, and in three months the reaction to the test was reported as negative.

There was no serorelapse or mucocutaneous relapse during the six months the patient was under observation. She then left the city and became unavailable for follow-up observation.

SUMMARY

A case of secondary syphilis is reported, in which vesicular lesions occurred on the palms of a young white woman. Treponema pallidum organisms were found on dark-field examination of the vesicular fluid.

SIMPLE TREATMENT OF PERIUNGUAL VERRUCAE

LAWRENCE FRANK, M.D.
BROOKLYN

Treatment of periungual verrucae is often a problem. Recurrences are frequent, and a radical approach sometimes results in nail deformity. Two years ago Dr. Charles Ritter [1] suggested an approach which he had found moderately successful. He used an occlusive dressing of adhesive tape and kept the verruca and the distal phalanx covered for a period of three to six weeks. At the end of this time the macerating effect often caused a disappearance of the wart. I tried this procedure, and my results were successful in about 40% of the patients so treated. However, the difficulty of keeping a dressing on the finger for so long a period made the treatment impractical. In an attempt to shorten the time required for occlusion I applied first 90% trichloroacetic acid to the verruca, after this I tried an application of liquid phenol, and then occluded the verruca completely with an adhesive dressing. I found that when the adhesive was removed after one week the wart was dried and adhered to the adhesive and the entire wart came off with the adhesive dressing, leaving a clean bed beneath. Occasionally, when the wart did not come off with the adhesive, simple curettage was sufficient to remove the remaining dried and crumbly material which was all that remained. The patients frequently complained of pain on the second or third day following the treatment, but in only two patients was the pain severe enough to require removal of the occlusive dressing. In one patient an infection developed locally which responded to simple hot soaks.

Seventeen patients with a total of 22 periungual verrucae were treated with this method. Of the 22 verrucae 16 were removed in one week with no recurrence. The procedure is simple, and the results justify its trial in all cases of periungual verrucae. The same treatment on verrucae vulgares not periungual in location failed in all cases treated, possibly because a proper occlusion could not be obtained.

55 Rugby Rd. (26)

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1. Ritter, C.: Personal communication to the author.

CORTICOTROPIN (ACTH) IN THE TREATMENT OF LEPRA REACTION

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ROCHESTER, MINN.
LAURO DE SOUZA LIMA, M.D.
AND
LINDA NAHAS, M.D.
SAO PAULO, BRAZIL

Since sulfone drugs were introduced in the treatment of leprosy the evolution of this disease has been considerably modified, but, unfortunately, the episodes of lepra reaction which occur in the course of the lepromatous form are not influenced by sulfone therapy. The lepra-reaction syndrome is characterized by erythema nodosum, neuritis, joint and muscle pains, and constitutional symptoms. Recent published reports indicate a favorable influence of corticotropin (ACTH) and cortisone on the lepra reaction. Johansen and Erickson,[1] in a review of the treatment of leprosy, stated that cortisone seemed to be of value in the treatment of this reaction and

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1. Johansen, F. A., and Erickson, P. T.: Current Status of Therapy in Leprosy, J. A. M. A. **144**:985-989 (Nov. 18) 1950.

leprous iridocyclitis, and Roche and his associates [2] also believe that corticotropin controls the lepra reaction and should prove a useful adjunct in the treatment of leprosy.

The following cases are reported to show the results of the use of corticotropin on the lepra reaction. The six cases are those of patients hospitalized in Padre Bento Sanatorium, São Paulo, Brazil. Each patient had the lepromatous form of leprosy, with recurrent attacks of lepra reaction, and had received a long course of sulfone therapy. When we started to use corticotropin, there were no reports in the literature about its use in the treatment of the lepra reaction, and, since only a limited amount of the drug was available, different dosages were employed. Corticotropin was administered every eight hours, and the duration of the treatment varied from 4 to 34 days. The patients were observed for six months after they had finished the course of treatment.

REPORT OF CASES

Case 1.—A young male patient who had been in the sanatorium since Feb. 3, 1948, had a lepromatous form of leprosy with recurrent attacks of erythema nodosum, joint pains, and neuritis. A long course of sulfone therapy had not influenced the attacks of lepra reaction. The sulfone treatment was stopped. A preliminary injection of 15 mg. of corticotropin produced a decrease of 30% in the level of the eosinophils after four hours. A total dose of 755.5 mg. of corticotropin was administered in 34 days, starting with 30 mg. per day, then 22.5 mg., and, finally, 15 mg. per day. Following treatment there was improvement in his general condition, with disappearance of the joint pains and neuritis. The cutaneous features were not changed. Six months after the treatment the patient continued to present attacks of lepra reaction.

Case 2.—A girl had been in the sanatorium since March 9, 1948, with a lepromatous form of the disease. While receiving sulfone treatment she had recurrent attacks of nodules, joint pains, and neuritis. The eosinophilic level dropped 41% four hours after 15 mg. of corticotropin was administered. The patient received a total dose of 325.5 mg. of the hormone in 17 days, starting with 30 mg. a day and followed by 15 and 10.5 mg. a day. Improvement of the neuritis, joint pains, and general condition was noted during the course of corticotropin; however, there were no modifications of the cutaneous lesions. The symptomatology recurred after the treatment was stopped.

Case 3.—A man patient had been hospitalized since Feb. 3, 1941. He also had the lepromatous type of the disease, with continuous attacks of lepra reaction which became worse after the administration of sulfones. The level of eosinophils four hours after the injection of 25 mg. of corticotropin showed a decrease of 64%. The patient received 220 mg. of the hormone in five days, with improvement of the general symptomatology but without alteration in the cutaneous aspect. The symptomatology recurred after the use of corticotropin was stopped.

Case 4.—A man patient had been hospitalized since Nov. 7, 1947. He had lepromatous leprosy with recurrent erythema nodosum and extremely severe neuritis which had not been influenced by sulfone treatment. Eosinophils decreased 74% four hours after the administration of 25 mg. of corticotropin. The treatment was started with 45 mg. per day and was followed by 30 mg. and 25 mg. per day. The total dose was 965 mg. in 32 days. The course of corticotropin was followed by improvement of the general condition, with sufficient relief of the pains to make analgesics unnecessary. There was also improvement of the cutaneous lesions, evidenced by a decrease in the infiltration. Six months after the treatment the symptomatology had not recurred, and the cutaneous features were still improved.

Case 5.—A woman patient had been hospitalized since Sept. 8, 1949. She had lepromatous leprosy with continuous attacks of lepra reaction, which had not been influenced by therapy. Eosinophiles decreased 80% four hours after 25 mg. of corticotropin was administered. She received 200 mg. of the hormone in four days, which gave relief of pains during the treatment but did not alter the cutaneous lesions.

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2. Roche, M.; Convit, J.; Medina, J. A., and Blomenfeld, E.: The Effects of Adrenocorticotropic Hormone (ACTH) in Lepromatous Lepra Reactions, Internat. J. Leprosy **19**:137-145 (April-June) 1951.

CASE 6.—A man who had been hospitalized since May 4, 1946, had a lepromatous form of leprosy with continuous attacks of lepra reaction with severe pains and neuritis. Eosinophilic response after a dose of 25 mg. was 58%. Corticotropin was administered for 14 days, the total dose being 460 mg. This patient also reported relief of pains and neuritis during the course of treatment, but no alteration in the cutaneous lesions was observed. The neuritis recurred four months after the treatment was finished.

SUMMARY AND CONCLUSIONS

Six patients with lepromatous leprosy, who had recurrent attacks of lepra reaction while receiving sulfone therapy, were subsequently treated with corticotropin (ACTH). The course of treatment varied in length from 4 to 34 days. All patients showed improvement in their general condition during the treatment. In one case there was a pronounced and immediate relief of the joint pains and neuritis, with some improvement in the cutaneous lesions. In the other cases no change in the skin lesions was noted. All cases were observed for a period of six months after the course of corticotropin. The hormone may be helpful in lepra reaction. The use of large doses given over a longer period, together with sulfone therapy, should be investigated.

Mayo Clinic (Dr. Sampaio).

SKIN REACTIONS TO HAIR DYES

A. J. REICHES, M.D.
ST. LOUIS

Hair dyes have been used by man since ancient times. However, the recent popularization of hair dyeing has greatly broadened this field of cosmetology. Up-to-date home hair dyes and practically all the beauty-parlor hair-dye preparations[1] are of the so-called oxidation or penetration type of hair coloring. This hair dye is basically a solution of *p*-phenylenediamine.

I am reporting three cases of cutaneous irritation of the scalp from the use of an oxidation type of hair dye. Although untoward reactions are apparently not numerous, the occasional occurrence of a severe reaction justifies the report of the following cases.

REPORT OF CASES

In two of the three cases herein reported the hair coloring was applied at beauty parlors, and in the third it was applied at home.

CASE 1.—M. S., a white woman aged 42, had one brand of an oxidation-type hair dye applied to her scalp at a local beauty parlor and immediately noticed a burning sensation on her scalp. When examined the following morning, she had small patches of a vesiculopustular dermatitis covering most of the scalp and the backs of both ears. The condition responded to local medications.

CASE 2.—L. R., a white woman aged 43, had an oxidation-type hair dye applied to her scalp at her beauty salon and told of immediately having a burning sensation on her scalp. When examined two days later, she showed patches of a papulopustular dermatitis covering large areas of the scalp. The dermatitis cleared with medications.

CASE 3.—R. W., a white woman 27 years of age, applied a home-type hair dye to her scalp and reported the development of sores on her scalp shortly after. When seen two days after use of the hair dye, she had a papulopustular dermatitis on her scalp which responded to local therapy.

COMMENT

The trade differentiates between hair rinses and hair dyes. Hair rinse is the term used for various certified colorings usually prepared in an organic base, such as citric or tartaric acid.

1. Personal communication from dye manufacturer to the author.

There are three general types of hair dyes [2]—the oxidation, the metallic salt, and the vegetable (natural color) dyes. Neither the metallic salt nor the vegetable dye is as satisfactory as the penetration or oxidation type. The oxidation type, which is a *p*-phenylenediamine dye, has almost replaced other hair dyes in beauty parlors and now is widely used by women who color their own hair. The metallic salt dyes are composed of salts of antimony, lead, copper, iron, nickel, and silver. Lead-sulfur hair coloring is an example of such a dye. The vegetable-type dyes are henna, henna compound, walnut, etc. Mixtures of vegetable coloring materials with metallic solutions and even mixtures with the modified *p*-phenylenediamine preparations also have been marketed.

The oxidation hair dye offers colors that closely resemble normal hair pigmentation. The coloring is not a hair coating, such as results from use of metallic or vegetable dyes, but actually penetrates the outer cuticle of the hair shaft and enters the cortex. The dye is composed of *p*-phenylenediamine, or some modification of this agent, and synthetic dye materials which are in an alkaline solution. Hydrogen peroxide is commonly added to increase the oxidation reaction. The final color of the hair depends not only on the color of the tinting liquid but also on the amount of oxygen entering the reaction. Phenols are often added to prevent the formation of an insoluble "Bandrowski base."

It is of interest that even though the basis of this dye is *p*-phenylenediamine, which has had a long history of being a potent skin sensitizer, not too many cases of hypersensitization have been reported after the use of the oxidation type of hair dye. One must, however, be on the alert for such hypersensitization. A patch test, which was not used in these three reported cases, such as the application of a small amount of dye to the skin behind the ear for 24 to 48 hours before each hair dye, is of definite value in testing for hypersensitization to this dye.

SUMMARY

Three cases of cutaneous irritation to the oxidation type of hair dye, which is largely replacing metallic salt and vegetable (natural color) hair dyes, are reported.

The oxidation hair dye depends on the action of *p*-phenylenediamine or some modification of this agent.

2. Compounder's Note, Drug & Cosmetic Industry (No. 2) **49**:205-207, 1941.

DISCOVERY OF PODOPHYLLUM RESIN

SAMUEL J. ZAKON, M.D.
CHICAGO

The recent introduction of the use of podophyllum in the treatment of condyloma accuminata,[1] its possible cancerocidal potentialities, and its usefulness as a tool for cytologic study make it, according to Sullivan,[2] a drug of considerable interest. However, the story of podophyllum would not be complete without recalling its humble beginning. John Uri Lloyd [3] (1849-1936), the famous pharmaceutical chemist of Cincinnati, gives the following account of the discovery of podophyllum.[4]

From the Department of Dermatology, Northwestern University Medical School (Herbert Rattner, M.D., Chairman).

1. Kaplan, I. W.: Condyloma Accuminata, New Orleans M. & S. J. **94**:338, 1942.

2. Sullivan, M.: Podophyllotoxin, Arch. Dermat. & Syph. **60**:1 (July) 1949.

3. Lloyd, J. U.: Remington's Practice of Pharmacy, ed. 9, Easton, Pa., Mack Publishing Company, 1948, p. 15.

4. Loyd, J. U.: Bulletin 12, Lloyd Library of Botany, Pharmacy and Materia Medica, Pharmacy, Series 2, Cincinnati, 1910.

In 1835 Dr. John King accidentally discovered the resin of podophyllum. Its discovery and the serious consequences following the blunder of its initial administration is best told by the discoverer in a letter to John Uri Lloyd:

North Bend, Ohio, June 14, 1887.

My dear Sir,

At your urgent request, I will endeavor to give you a brief account of the discovery of the Resin of Podophyllum Root, more commonly known as "podophyllin." My introduction to it was entirely accidental, and attended with very unpleasant circumstances.

In the fall of 1837 [The date was 1835, see *Philosophical Journal and Transactions* **1**:157-166, 1844.], I think it was, knowing nothing of this resin, an attempt was made to prepare a hydro-alcoholic extract from some fourty pounds of the coarsely powdered Podophyllum Root. A portion of alcohol having been distilled over from the root tincture, water was added to the remaining tincture, the intention being to evaporate this diluted tincture that a hydro-alcoholic extract might be had, but night coming on, the process of evaporation was postponed until the following day. On the next morning, while stirring the cold mixture, numerous pieces of a dark, somewhat porous and rather brittle body were found in the fluid. Many were the surmises as to what they were, and the query arose as to their value, if any, as a medicinal agent.

In the midst of these speculations, a young lady about seventeen, who was present, complained of feeling ill. Having no idea of the intense activity of the article just discovered, I administered about twelve or fifteen grains. Nothing further was thought of the matter until an hour afterward when my attention was called to her condition. She was in severe pain and distress, cramps in the stomach and extremities, pulse was small and feeble, extremities cold, excessive vomiting and hypercatharsis, and apparently sinking rapidly. Her condition greatly resembled that of a person suffering from an attack of Asiatic cholera. To say that I was greatly alarmed would but feebly describe my mental condition. I ran to secure the aid of two or three professional friends, but could find none of them in their offices. Then I ran back again, trembling over what the consequences might be, and thinking out a course of treatment to pursue. A princely fortune could not induce me to undergo a repetition of such condition.

By the time I reached the patient, I had become more calm. A half-saturated, aqueous solution of potash saleratus was given in tablespoonful doses, every ten minutes, several doses being administered before the stomach would retain it; subsequently, the intervals between the doses were lengthened. Sinapisms were applied to the wrists and ankles; a fomentation of bitter herbs as hot as could be borne was applied over the stomach and abdomen, changing it as often as required. In about an hour the extremities became warm, and a general perspiration soon followed, with diminishing suffering and a partial return to a feeling of health and strength. In about an hour or two succeeding the improvement, the sinapisms were removed, an infusion of slippery-elm bark was ordered to be drunk freely, and about eight grains of the Compound Powder of Ipecacuanha and Opium were given every three hours. The next morning she was decidedly better.

In the course of the second day her friends allowed her to have a little soup, which was followed by a serious gastro-enteritic inflammation. The fomentations and sinapisms were repeated, and the Diaphoretic Powders continued, as well as the slippery-elm infusion, to which some prepared charcoal was added, not daring to prescribe a more active laxative. By perseverence in this course, the patient recovered in six to seven days, but, unfortunately, with some chronic gastro-enteritic abnormal condition, that remained for many years. From this experience I was so influenced that I feared to use any of the remainder of the resin until at least eighteen months had passed, when I ventured a repetition of its use, but in much smaller quantity, and with most excellent results.

There, my dear Professor, you have in a nutshell my discovery, which led to further investigations, resulting in the obtainment of more or less active principles from other medicinal plants.

In closing, permit me to add that I have found your medicinal preparations, resinoids, concentrated remedies, etc., that I have had from you since you have entered into the manufacture, to be reliable and worthy of confidence.

Yours with respect,
John King, M.D.

For over 100 years podophyllum was used mainly as a vegetable cathartic of dubious value until Kaplan [1] introduced it as a topical remedy for condyloma accuminata. Its discovery in 1835 by King is an interesting paragraph in the history of pioneer medicine of the Midwest,[5] where the doctor was often unlearned but bold and the patient was brave and the hero. This is a part of our heritage and the seeds from which our contemporary American medicine grew.

1 N. Pulaski Rd. (24)

5. Pickard, M. E., and Buley, R. C.: The Midwest Pioneer: His Ills, Cures, and Doctors. New York, Henry Schuman, Inc., Publishers, 1946.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

Benjamin Levine, M.D., *President*
Herbert H. Johnson, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
March 22, 1951

Pseudoxanthoma Elasticum, Angioid Streaks of Retina, and Osteitis Deformans. Presented by Dr. C. W. Woodcock.

C. H., a white man, aged 54, was admitted to the Dental Service at Crile Veterans Administration Hospital on Nov. 14, 1950, with severe pain and swelling in the mandible.

The past history revealed that the diagnosis of Paget's disease had been made in 1932. From May to October, 1948, the patient had been hospitalized for a compound fracture of the upper third of the left femur. Renal calculi were discovered on that admission.

Physical examination on this admission revealed a white man with extreme kyphosis and marked enlargement of the head. Angioid streaks were noted in both retinae. There was diminished auditory acuity bilaterally. Swelling of the left lower jaw and a draining sinus in the left lower gum were noted. The chest was emphysematous, with marked dorsal kyphosis. There was lateral and anterior bowing of both lower legs.

On admission, a hemogram, urogram, and a serologic test for syphilis presented no abnormalities. Serum calcium and phosphorus and acid phosphatase determinations were within normal limits. Roentgenograms of the spine, pelvis, skull, and chest revealed the typical bony changes of osteitis deformans, with generalized and spotty osteoporosis, irregular areas of chalky increase in density, and increased and coarsened trabeculation.

A dermatologic consultation was obtained because of seborrheic dermatitis of the face and scalp. In addition to this eruption of the face and scalp, pseudoxanthoma elasticum of the skin in the axillae and angioid streaks in the retinae were also noted.

The patient was seen by the consulting ophthalmologist, who confirmed the diagnosis of angioid streaks of the retinae.

DISCUSSION

Dr. H. H. Johnson: There have been a number of cases of Paget's disease with angioid streaks reported; also, as we are all aware, patients with pseudoxanthoma elasticum usually have angioid streaks of the retinae. This is a case of Paget's disease, pseudoxanthoma, and angioid streaks of the retinae. As we know, pseudoxanthoma is believed to be a recessive hereditary disease. It makes one wonder whether osteitis deformans may not be a disturbance of the elastic tissue in the osseous structures, causing the changes seen there. Certainly in both conditions the retinae may have some disturbance in elastic tissue.

Pemphigus Vegetans: Responding Favorably to Corticotropin Therapy. Presented by Dr. George M. Stroud, Dr. H. H. Bremers, and Dr. U. W. Leavell for Dr. H. N. Cole and Dr. J. R. Driver.

Case for Diagnosis: Periarteritis Nodosa? Presented by Dr. H. H. Bremers and Dr. U. W. Leavell for Dr. H. N. Cole and Dr. J. R. Driver.

Benjamin Levine, M.D., *President*
Herbert H. Johnson, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
May 31, 1951

Histoplasmosis. Presented by Dr. Harold R. Schwartz (by invitation), Akron.

E. A., a 56-year-old white man, entered the City Hospital of Akron because the right great toe had been painful and swollen for four weeks. Seven months previously a painful swelling of the skin had appeared on the outer aspect of the left arm. This lump soon broke down and formed a draining ulcer. A year ago an abscess appeared on the left lateral thigh, at the site of injection of a penicillin-in-wax preparation. Incision of this abscess left a persistent purulent drainage.

The patient came to the United States from Macedonia in 1914, settled in Ohio, and has not left the state since then. From 1919 to 1931 he worked in a clay insulator factory. Since 1946

he has been known to have silicosis but has had no respiratory symptoms other than an occasional nonproductive cough.

On physical examination, the patient does not appear ill. The great toe of the right foot is hot, swollen, and tender. A shallow, grayish-white ulcer, 22 by 13 mm., on the outer aspect of the left arm exhibits purulent drainage. A 3-in. (7.6-cm.) incision, with a small amount of purulent drainage, is present on the outer aspect of the left thigh.

Roentgen studies of the right great toe revealed osteomyelitis, with complete destruction of the proximal phalanx. A roentgenogram of the lungs showed pneumonic infiltration, with suppuration and areas of breakdown in the right upper lobe, superimposed on far-advanced pneumoconiosis. There was no roentgen evidence of osteomyelitis involving the left humerus.

Complete blood counts have been normal. Skin tests with old tuberculin have given negative reactions with 1:10,000 dilution but positive reactions with 1:1,000 dilution. A coccidioidin skin test reaction was negative.

Histopathologic study of skin tissue excised from the left arm and smear and culture of draining exudate from the right great toe both revealed Histoplasma capsulatum. Repeated examinations of sputum and gastric contents, with smears, cultures, and guinea-pig inoculations, have been negative for Histoplasma and acid-fast organisms.

The patient's course of illness is stationary. He has never appeared acutely ill. A low-grade fever, present on admission, disappeared after incision of the right great toe. Treatment with potassium permanganate soaks, terramycin ointment dressings, and stibamine glucoside (neostam®) have been of no value.

DISCUSSION

DR. H. N. COLE: I believe that this is the first such case shown before the Cleveland Dermatological Society.

DR. E. S. HALLINGER: Dr. Curtis recently stressed the importance of the relationship of Hodgkin's disease and histoplasmosis.

Scleroderma of the Left Thigh and Left Ankle. Presented by DR. FRANK M. MCDONALD, Akron.

J. G., a 34-year-old white man, presents a cutaneous disease involving the left ankle and left thigh of 15 months' duration. The lesions looked like bruises at the onset, and the appearance has changed little, except for their increasing in extent. Both areas enlarged slowly and have been asymptomatic at all times.

On the inner aspect of the left heel and ankle there is a discrete, circinate, purplish-brown, atrophic macule with reddish-brown edges, measuring 5 cm. in diameter. The middle two-thirds of the outer aspect of the left thigh exhibits an area of brownish-yellow discoloration, the surface of which is smooth and semiglistening, with pronounced induration on palpation.

Blood count, results of urinalysis, the sedimentation rate, and the serum calcium and fasting blood sugar levels were normal. The basal metabolic rate was —14%.

Histopathologic examination of skin specimens from both thigh and ankle showed the lesions to be similar. The epidermis was atrophic. There were extensive hyalinization in the corium and chronic inflammatory infiltrate around the accessory skin structures.

Treatment has been limited to intramuscular injections of vitamin E, 200 mg. in oil, at 1- or 2-week intervals, for eight visits over a 10-week period, plus vitamin B complex (becotin,® three capsules daily) by mouth. The ankle lesion is improved 60%, and the thigh lesions are softer, showing perhaps 30% improvement.

Circumscribed Scleroderma of the Face (Morphea); Facial Hemiatrophy. Presented by DR. A. L. LEIBY, Akron.

J. C., an 8-year-old white girl, was first seen two years ago. Ten months previously her mother noticed on the right cheek white spots which continued to enlarge. Physical examination revealed a thickened white patch, ½ in. (1.3 cm.) wide, on the anterior aspect of the right cheek, just below the eye. This white line swung down to a point just above the right jaw and then posteriorly back up to the temple and beyond the hairline. Here, at the temple, the color of the line became ivory. There was partial loss of hair on the right temple. The contour of the right cheek was much less rounded than that of the left.

Microscopic examination of a skin biopsy specimen revealed the following: Within the cutis the collagen bundles in the subepidermic region were edematous, and in places sclerosis was seen.

There was a mild fibroblastic reaction. There appeared to be a loss of adnexa, and in the center of the section there was a dilated follicle, filled with horny plugs. The epidermis was flattened but showed no important change.

The patient was treated with vitamin E capsules, a vitamin D preparation, multivitamin tablets, and vitamin E injections. There has been improvement in the indurated areas. The affected portion in the temporal area of the scalp cleared, and there was full regrowth of hair. The patient now presents a pigmented area on the right cheek, which is flatter in contour than the left. There are scattered telangiectases. There is a small depressed area on the right upper lip. The teeth are erupting normally.

DISCUSSION ON PRECEDING TWO CASES

DR. J. R. DRIVER: There was considerable asymmetry of the cheeks, and perhaps the child does have morphea, but the appearance gave me the impression that there was an underlying lipodystrophy.

DR. I. L. SCHONBERG: All but the infiltrated lesions in the first case could be accepted under the diagnosis of atrophic lichen planus, including the lesion on the ankle.

DR. J. R. DRIVER: Of course, he has scleroderma, too.

DR. F. M. MCDONALD, Akron: The point was that the atrophic lichen planus still shows lesions which pathologically may be interpreted as being scleroderma.

Sarcoid (Boeck). Presented by DR. A. L. LEIBY, Akron.
Nevus Pigmentosus et Pilosus. Presented by DR. H. A. HAYNES JR., Akron.
Pityriasis Rubra Pilaris; Oil Folliculitis. Presented by DR. H. A. HAYNES JR., Akron.
Case for Diagnosis: Erythema Elevatum Diutinum? Rheumatic Nodules? Presented by DR. A. L. LEIBY, Akron.
Necrobiosis Lipoidica Diabeticorum. Presented by DR. A. L. LEIBY, Akron.
Lichen Sclerosus et Atrophicus. Presented by DR. FRANK MCDONALD, Akron.
Necrobiosis Lipoidica Diabeticorum. Presented by DR. FRANK MCDONALD, Akron.
Granuloma Inguinale (?); Extensive Infectious Granuloma (?). Presented by DR. A. L. LEIBY, Akron.
Case for Diagnosis: Lymphoblastoma with Cornifying Squamous Carcinoma of the Shoulder? Prurigo Nodularis of the Posterior Neck? Presented by DR. H. A. HAYNES JR., Akron.
Epidermolysis Bullosa in Third Generation. Presented by DR. H. A. HAYNES JR., Akron.
Idiopathic Multiple Hemorrhagic Sarcoma of Kaposi. Presented by DR. EMERSON GILLESPIE, Canton.

MANHATTAN DERMATOLOGIC SOCIETY

Paul E. Bechet, M.D., *Co-President*
Isadore Rosen, M.D., *Co-President*
George M. Lewis, M.D., *Secretary*
April 10, 1951

Epidermolysis Bullosa, Probably Produced by Sulfonamides. Presented by DR. DAVID BLOOM.

E. S., a Negro woman aged 44, was first seen at the New York Skin and Cancer Unit of the University Hospital in September, 1949, complaining of an eruption of more than two years' duration. The patient had eight brothers and one sister, one of whom died at the age of 23 with "lung trouble." Six died in infancy, one having had "skin trouble." No other member of the family had any cutaneous disease. The parents were not related.

During 1944, 1946, and 1947, the patient suffered from bronchitis, for which she received sulfadiazine, each time in an initial dose of 4 gm., followed by 1 gm. every four hours for five days. At the end of 1946 a pruritic urticarial eruption developed which persisted until June, 1949, when ulcers appeared in the mouth. Somewhat later a generalized bullous eruption developed, for which she was at New York City Hospital from July, 1947, to January, 1948. While there, she received, among other medication, 90 doses of acetarsone. The eruption gradually assumed the appearance of epidermolysis bullosa.

When seen at the Skin and Cancer Unit in December, 1949, the patient showed superficial ulcers and whitish spots on the tongue and oral mucosa, in addition to a few pea-sized bullae on the elbows, fingers, and hands and depigmented scars and spots on the lower extremities and trunk. In March, 1951, she presented a few hemorrhagic bullae on the hands, on the inner aspect of the thighs, and on the second right toe and one large broken bulla in the gluteal region. The rest of the skin showed scars; these were particularly noticeable on the elbows, knuckles, backs of the hands and fingers, the knees, and over the Achilles tendon. On the right buccal mucosa there was a leucoplakia-like lesion. Most of the fingernails and toenails were gone, and others were dystrophic and about to fall off.

Routine laboratory examinations gave normal findings except for an increased erythrocyte sedimentation rate.

DISCUSSION

DR. FRANK C. COMBES: I agree with the diagnosis; there is no reason that the sulfonamides can't be the trigger mechanism which precipitates the attacks. Alcoholic bouts frequently do the same. It is explained by the toxic effect on the liver, which seems to precipitate the cutaneous lesions.

DR. ORLANDO CANIZARES: I agree with the diagnosis. I presented at the last meeting a man with a bullous eruption of this type, and there was a question of the sulfonamide drugs being responsible and of possible multiple myeloma. He is still in the hospital and still showing bullae; his condition is going downhill fairly fast.

DR. PERRY SACHS: I was wondering if readministration had been tried, and what its results would be. Also, it should be noted that the patient claimed that a sibling had a persistent bullous eruption of the hands.

DR. FRANK C. COMBES: I didn't mean that it was a bullous eruption in the sense of dermatitis medicamentosa, but that there was probably a familial history of epidermolysis bullosa and that the sulfonamides could act as a precipitating factor, as alcohol does. It doesn't require the readministration of alcohol but will go on for years.

DR. SAMUEL M. PECK: One would expect that the discontinuance of use of the drug would result in the disappearance of the lesions, at least after several months. However, we have a modern example in quinacrine hydrochloride (atabrine® dihydrochloride); the dermatitis resulting from this drug may last more than a year, and we know from our experience with arsenic in the past that keratoses may be seen 20 years after the ingestion of inorganic arsenicals.

DR. WILBERT SACHS: I believe arsenic may be retained for many years. I was under the impression that the sulfonamides are not retained.

DR. PAUL E. BECHET, Elizabeth, N. J.: The appearance is typical of ordinary epidermolysis bullosa. I have never noted severe bullous eruptions resembling epidermolysis bullosa following use of sulfonamide drugs. This patient also shows the typical scarring of epidermolysis bullosa.

DR. DAVID BLOOM: We know that epidermolysis bullosa dystrophica may appear late in life. Although in the individual case there may be no proof of hereditary origin (no other members of the family being affected and absence of consanguinity in the parents), we are justified in assuming that it is nevertheless hereditary in nature. This is clear to anyone who is acquainted with the elementary principles of genetics. However, we know also that hereditary abnormalities may be imitated by nonhereditary factors: For instance, porphyria may be produced by liver damage due to alcohol, and keratosis palmaris et plantaris may be produced by arsenic. Thus, the cases of epidermolysis bullosa dystrophica appearing late in life may be produced by nonhereditary factors. Siemens has reported a case which he believed to be due to arsenic (*Arch. Dermat. u. Syph.* **149**:71, 1925). This case, like several others I have observed and seen in society meetings, is due, I believe, to an irreversible damage of the skin produced by sulfonamides.

Case for Diagnosis: Lichen Planus of the Mouth? Presented by DR. ORLANDO CANIZARES.

J. L., a man aged 28, is presented from the Bronx Veterans Administration Hospital with the complaint of a sore mouth for the past six weeks. The patient has renal tuberculosis and has been receiving *p*-aminosalicylic acid and streptomycin since January, 1951.

There is a white, somewhat opalescent, smooth, irregular network covering the mucous membrane of the cheeks and the tongue. On the under surface of the tongue, the palate, and buccal mucous membrane there are some bright red, superficial ulcerations. On the posterior pharyngeal wall whitish patches are visible.

Blood studies gave normal results. Urinalysis revealed albumin (1+) and sugar (1+). Biopsy of the mucous membrane showed characteristics consistent with a diagnosis of lichen planus. Scrapings for Candida did not yield the organism.

The patient has had symptomatic relief with the use of "listerine" (a weak antiseptic solution similar to N. F. antiseptic solution) gargle and hydrogen peroxide mouth wash.

NOTE.—Since biopsy of the mouth lesions, the ulcers have healed.

DISCUSSION

DR. ISADORE ROSEN: I think this patient is suffering from a bullous drug eruption involving the mucous membrane of the mouth. Bullous eruptions in the mouth are often seen after the ingestion of drugs of the barbiturate group. The clinical features present are produced by bullous lesions in the various stages of development and repair. There is only one area on the right cheek which suggests lichen planus, but I believe the whole process is due to the ingestion of drugs.

DR. DAVID BLOOM: The stomatitis of this patient does not appear to be that of lichen planus, but drugs should be suspected as causative agents.

DR. FRANK C. COMBES: Taking the whole eruption as one, it suggests to me lupus erythematosus more than anything else. If there were not a well-defined serrated edge on the lips along the vermilion border, I should agree with Dr. Rosen regarding a bullous eruption of the oral mucosa. I don't see any feature that suggests lichen planus.

DR. WILBERT SACHS: The slide certainly suggests the possibility of lichen planus. The epidermis is acanthotic; the granular layer is increased, and there is no evidence in the slide of bullous lesions. I didn't study it long, but if I had to make a diagnosis I would say lichen planus.

DR. GEORGE M. LEWIS: The most important thing is that it is not leucoplakia, which many so-called cancer experts seem to have difficulty in recognizing. The clinical features seemed suggestive of Candida infection, but two negative scrapings pretty well rule that out. I am, therefore, inclined to agree with the presenter's diagnosis.

DR. ORLANDO CANIZARES: The first impression was that it was moniliasis; we used methylrosaniline chloride (gentian violet), but there was no improvement, and repeated slide examinations gave negative results. I am inclined to think that drugs may have something to do with it, but I have never seen the medicaments he has received cause this type of eruption. He has taken no drugs other than those mentioned. I shall follow the suggestion of Dr. Costello and treat this as lichen planus.

NOTE.—Three weeks later the patient exhibited typical lesions of lichen planus of the glans penis.

Atopic Eczema. Presented by DR. GEORGE M. LEWIS.

Case for Diagnosis: Scleroderma? Sclerodermatomyositis? Muscular Dystrophy. Presented by DR. ORLANDO CANIZARES.

Case for Diagnosis: Fibromatous Nevus? Presented by DR. NATHAN SOBEL.

MINNESOTA DERMATOLOGIC SOCIETY

Stephan Epstein, M.D., *President*

Harold G. Ravits, M.D., *Secretary*

Nov. 16, 1951

Porphyria (Mixed Type), Hepatic Form. Presented by DR. F. W. LYNCH, St. Paul.

Mrs. M. C., aged 66 years, first noted an eruption on the hands and face in 1949, at which time it was thought to be due to handling of flowers. Subsequently there were recurrent blisters and some scaling of the hands and face after relatively minor thermal and mechanical injuries. The eruption disappeared during the following winter. In the spring of 1950 the cutaneous symptoms recurred, and there were intermittent passages of dark red urine. The eruption recurred in the summer of 1951, and the urine was then red most of the time.

There is a family history of similar eruptions, but as yet no knowledge has been obtained of the condition of the urine or of any systemic manifestations in family members. The patient has had no particular abdominal pain or nervous manifestations.

She was recently studied on the service of Dr. Cecil Watson at the University of Minnesota Hospitals with the following findings: Direct bilirubin measured 0.2 mg., with a total of 1.4 mg., per 100 cc. Serum proteins totaled 7.2 gm., with 2.9 gm. of albumin and 4.3 gm. of globulin. Cephalin-cholesterol flocculation was 1+, thymol turbidity, 6 units, and zinc turbidity, 12 units. The hepatic and splenic enlargement and the slightly abnormal results on function tests pointed strongly to functional impairment of the liver. Gamma uroporphyrin excretion was between 7 and 26 mg. per day. Coproporphyrin excretion was 300 to 1,400 mg. per day. Studies of bone marrow and erythrocytes gave normal values for coproporphyrin and protoporphyrin,

whereas uroporphyrin was not found. Biopsy followed by special studies showed in the liver 3 mg. of uroporphyrin per 100 mg. This is the highest value Dr. Watson has ever found in a patient with hepatic porphyria.

Treatment with oral administration of riboflavin has been started recently.

DISCUSSION

Dr. John Krafchuk, Minneapolis: The classification of the porphyrias has heretofore included three groups: the congenital light-sensitive type, the acute intermittent type, and the mixed type combining features of both. Recent investigations by members of the Department of Medicine at the University of Minnesota Hospitals have indicated certain new concepts with regard to classification. On examination with the fluorescent microscope some patients with porphyria demonstrate heavy concentrations of porphyrins in the bone marrow with normal results on liver tests; others demonstrate the reverse, with hepatic tissue showing very heavy fluorescence and normal bone marrow. To date, the bone marrow demonstrates abnormal porphyrin levels in the congenital light-sensitive type, the liver in the other two types. In this case, material from the liver biopsy specimen showed heavy fluorescence. Dr. Watson and his group have had experience in treating this type of condition with vitamin B12, with improvement in symptoms and a decrease in the output of uroporphyrin and coproporphyrin. It may be anticipated that similar benefit may be obtained in this case.

Dr. Julius Stone, Minneapolis: My colleagues and I have been gathering microscopic sections from cases of light-sensitivity dermatitis. These sections will be examined in an effort to find some fluorescent materials that may be etiologically related to sunlight eruption. We have nothing to report as yet.

Dr. Warren Macaulay, Fargo, N. D.: One possible explanation is that these persons excrete abnormal porphyrin only intermittently. Their urine is not always red. As a matter of fact, redness of the urine is of relatively infrequent occurrence. The skin lesions appear only intermittently, too. However, exposure to ultraviolet light during periods of abnormal porphyrin excretion does not, in my experience, necessarily lead to the development of new lesions.

Dr. Quentin Conwell, St. Paul: I saw one case of porphyria in my service overseas. Cold stress was the factor that precipitated this man's attack. He had no skin symptoms. He had red urine and gastrointestinal symptoms.

Dr. Francis Lynch, St. Paul: The course of a patient with porphyria depends upon the class of porphyria he has. The patient presented tonight has the hepatic type of the disease, and her course will depend upon the nature of the underlying hepatic disease or disturbance in liver function. Usually in the hepatic form of porphyria there are cirrhosis and frequent alcoholism, neither of which seems to be present in this case. Therefore, the prognosis may be favorable. I have here a photograph which shows fluorescent material in the liver in a similar case.

With reference to light sensitivity, the authorities on this disease freely admit that they have no satisfactory explanation for the association between photosensitivity and disturbed porphyrin metabolism. The type of porphyria presented here is spoken of as hepatic porphyria and also as the mixed type, meaning that such cases present some features of the congenital, light-sensitive, hydroa-type disease and some features of the intermittent acute type of porphyria. It is the intermittent course of one major form of porphyria which probably explains the abnormal response to light at one time and the failure to respond at another in cases belonging to the mixed group.

Pemphigus Vulgaris. Presented by Dr. Orville E. Ockuly, St. Paul.

Mr. V. G., aged 63 years, noted on April 15, 1951, the sudden onset of an eruption on the back, spreading rapidly to other areas. There is no history of previous eruption. He had difficulty in voiding for some years, with complete retention on several occasions. He had been taking "Doan's kidney pills" (labeled as a mixture of theobromine sodiosalicylate, extract uva ursi, extract of buchu, and vitamin A). He was given four injections of ivyol® (extract of purified active vesicant principle of Rhus toxicodendron) by his family physician, and wet packs were applied. Examination on May 31 revealed an extensive eruption over the trunk, neck, and extremities, consisting of numerous scattered bullae, some hemorrhagic, as well as indurated serpiginous plaques over the trunk, with less severe lesions on the extremities. On the fingers

were numerous vesicles, seemingly dyshidrotic in type. Pitting edema of the feet and legs was marked. The diagnosis of erythema-multiforme-like eruption was made originally, with the possibility of drugs as a provocative agent. During the following week new bullae kept appearing, with the result that on June 9 a diagnosis of pemphigus had to be made.

Pemphigus Vulgaris. Presented by DR. JOHN F. MADDEN, St. Paul.

DISCUSSION ON PRECEDING TWO CASES

DR. FRED BECKER, Duluth: My last two patients with pemphigus have just died after receiving about $1,000 worth of cortisone and corticotropin. In both the autopsy showed acute hemorrhagic pancreatitis. In a recent review of Dr. Brunsting's article on the use of corticotropin and cortisone in acute lupus erythematosus, I noticed that the postmortem studies on some of these patients also showed acute hemorrhagic pancreatitis. The pathologist says that the condition is seldom seen in patients who die of ordinary septic disease. I am wondering if this is a complication of steroid therapy. Has anyone else seen it? How do you keep these patients cured with cortisone and corticotropin therapy?

DR. ISADORE FISHER, Minneapolis: I am not familiar with the effects of steroids on the postmortem changes in pemphigus, nor am I familiar with the production of pancreatitis during the administration of steroids. I can say only that on review of all the cases of pemphigus with autopsy at the University of Minnesota Hospitals, it was noted none of them presented a specific picture of pancreatitis.

DR. FRANCIS LYNCH, St. Paul: These cases bring our attention to the unusual course so frequently followed by pemphigus in elderly persons. In Dr. Madden's patient we have the striking pruritus and the large number of small lesions, some of which have been vesicular and some of which have now become crusted. Earlier in Dr. Ockuly's patient smaller bullae and numerous tense vesicles were present, and there were then and still are numerous arcuate, somewhat urticarial papular lesions. I think these changes are often seen in older persons, though there are also numerous more classic forms of pemphigus in older persons. Dr. Ockuly's patient presents another interesting feature: the prolonged and severe vascular hypertension. We all know the tendency for adrenal damage in patients with pemphigus and the relation between the adrenal glands and hypertension; yet here we have a man with prolonged and severe pemphigus and with hypertension that is increasing rather than decreasing.

DR. SEBASTIÃO SAMPAIO, São Paulo, Brazil: We have in São Paulo, Brazil, an epidemic form of pemphigus, so-called *fogo selvagem*. Today we think that *fogo selvagem* is analogous to pemphigus foliaceus. Sometimes the differentiation among dermatitis herpetiformis, pemphigus foliaceus, and pemphigus vulgaris is very difficult. The condition of one of the patients presented today looks to me like a very severe form of dermatitis herpetiformis. I should like to know what the histopathologic character of the bullae is in this case. Civatte has pointed out a difference between the bullae of pemphigus vulgaris and those of dermatitis herpetiformis. Brazilian observers generally agree with Civatte, and this characteristic may be helpful in differentiating Duhring's dermatitis (dermatitis herpetiformis) from pemphigus.

DR. JOHN KRAFCHUK, Minneapolis: There are certain indications for the use of corticotropin intravenously rather than intramuscularly. In some persons intramuscular injection causes no decrease in circulating eosinophiles, even though subsequent intravenous administration results in profound decrease. It must be concluded in these persons that the adrenal glands are normally responsive and that corticotropin is either inactivated in the muscle or not absorbed. In several recent cases at the University Hospitals, clinical response paralleled this effect, in that corticotropin given intravenously was dramatically effective after large intramuscular dosages of corticotropin were without effect. Thus, if the intramuscular Thorn test shows inadequate eosinophile response, one would have to use either corticotropin or cortisone intravenously. In addition, by intravenous administration roughly one-tenth as much corticotropin is needed for comparable effect, with savings in costs and materials. The intravenous use of corticotropin also has an advantage in maintaining a steady high level in the blood, whereas with intramuscular injections a series of very high peaks is obtained, with intervening periods of very low or negative concentrations.

DR. ORVILLE OCKULY, St. Paul: The bullae in my patient with pemphigus covered the extremities and a large portion of the trunk and varied in size, some being as large as the palm of the hand. They were flaccid, and even the smaller bullae could be pushed along the skin. At

one time he was losing most of his skin. It was at that time that the cortisone administration was begun, and within two days there seemed to be no new bullae. The following week the bullae subsided, crusted over, dried, and pigmented. As soon as the dose of cortisone was decreased to 10 mg., there was an immediate onset of new bullae. About 10 days ago cortisone therapy was discontinued for one day, with a sudden onset again of numerous bullae, the residual of which you saw here today. At present the patient is receiving 200 mg. daily.

Urticaria Pigmentosa and Cutaneous Xanthomas. Presented by Dr. Francis W. Lynch, St. Paul.
Ehlers-Danlos Syndrome. Presented by Dr. John F. Madden, Dr. Harold G. Ravits, and Dr. Quentin Conwell, St. Paul.
Nonsuppurative Panniculitis. Presented by Dr. John F. Madden, St. Paul.
Diffuse Scleroderma. Presented by Dr. Francis W. Lynch, St. Paul.
Chronic Lupus Erythematosus. Presented by Dr. John F. Madden, St. Paul.
Lupus Erythematosus. Presented by Dr. Francis W. Lynch, St. Paul.
Lichen Planus and Lupus Erythematosus. Presented by Dr. Orville E. Ockuly, St. Paul.
Prurigo Nodularis. Presented by Dr. Harold G. Ravits, St. Paul.
Hemangioma (?); Pyogenic Granuloma (?). Presented by Dr. John F. Madden, Dr. Harold G. Ravits, and Dr. Quentin Conwell, St. Paul.
Granuloma Annulare. Presented by John F. Madden, St. Paul.
Keratoderma Punctata. Presented by Dr. Orville E. Ockuly, St. Paul.
Necrobiosis Lipoidica Diabeticorum. Presented by Dr. Francis W. Lynch, St. Paul.
Guttate Parapsoriasis. Presented by Dr. John F. Madden, St. Paul.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Paul Gross, M.D., *Chairman*

Anthony C. Cipollaro, M.D., *Secretary*

April 3, 1951

Tinea Capitis Due to Ectothrix Trichophyton. Presented by Dr. Maurice J. Costello for Dr. J. I. Singer, Bay Shore, N. Y.

J. F., a girl aged 3½ years, was first examined on March 12, 1951. There had been a pruritic scalp eruption for one week. The patient lives next door to an animal hospital and has contact with animals kept there. She has one brother, aged 2 years, whose scalp and skin were clear at that time.

In the center of the girl's scalp was an area of yellowish to white scaling or crusting. There were chains of enlarged cervical glands. There was no fluorescence under the Wood light. Microscopic examination of hairs revealed no fungi. Because of the history of contact with animals, cultures were made on Sabouraud's dextrose medium from hairs or scales. An ointment with ammoniated mercury and salicylic acid was prescribed. Growth was noted in the cultures at the end of one week.

The patient was reexamined in about 10 days and showed almost complete disappearance of the scale. There was an area 7 by 3 mm. in the center of the scalp which showed slight papulofollicular inflammation. Careful examination also showed broken hairs projecting a few millimeters above the surface of the scalp. These were interspersed with normal-appearing hairs. On March 20 her brother exhibited an erythematous papular patch of dermatitis about 1 in. (2.5 cm.) in diameter on the occiput.

Microscopic examination of the short broken hairs showed oval to rectangular spores about 4 μ in diameter, surrounding the surface of the hair. Many of these were in linear formation. The culture grew slowly and after nine days was 7 mm. in diameter. The color was white to gray. The center of the colony was elevated and had short aerial hyphae. Older colonies were velvety to powdery. Some convolutions are appearing in older colonies. Culture mount after three weeks showed many microconidia in clusters and singly on the hyphae. Many chlamydospores were also present.

DISCUSSION

Dr. George M. Lewis: The presenter should be congratulated on thinking of fungous infection with the atypical clinical features presented by this patient. The causative fungus is probably in the group of endothrix trichophytons, such as Trichophyton crateriforme. There are only a few of these cases in this part of the country, although recent reports indicate an increased incidence in Texas and other parts of the South and Far West. The lack of inflammation and the nonfluorescence of the hairs are points in favor of that diagnosis. The culture as presented was certainly in that group. Attempts at cure will probably be unsuccessful unless epilation is performed, as it is a very difficult organism to eradicate.

DR. JOSEPH I. SINGER (by invitation), Bay Shore, N. Y.: When I first examined the hair, and I spent considerable time doing so, I felt the spores were external to the hair shaft, although clinically and culturally the growth does not fit into an ectothrix type. I should like to give the culture more time to develop and report at a later meeting.

NOTE.—Growth of the infected hair on Sabouraud's dextrose medium developed into a typical Trichophyton tonsurans (crateriforme) culture. Examination of older infected hairs showed an endothrix distribution of spores.

Lupus Erythematosus, Chronic Disseminated Type, Showing a Dramatic Response to Testosterone Therapy. Presented by DR. MAURICE J. COSTELLO for DR. JOSEPH I. SINGER, Bay Shore, N. Y.

M. M., a woman aged 29, has had chronic discoid lupus erythematosus for seven years. The onset occurred on the face after a sunburn, and the lesions have been progressive. The patient also has diabetes mellitus. Soon after the onset she was treated with crude liver extract, bismuth, and gold preparations, use of each of which had to be stopped because of toxic reactions. In 1948 she was given quinine orally and subsequently dermatitis medicamentosa developed from it. On her admission to St. Clare's Hospital in July, 1948, this eruption was erroneously diagnosed as subacute dissemination of the lupus erythematosus. The patient was presented before this section a year ago with the above history.

Treatment for the lupus erythematosus has been as follows: From Feb. 2 to May 18, 1949, mixed tocopherols, 1,285 mg., were given intramuscularly. The lesions progressed, and the patient complained of nausea. From June 8 to Nov. 16, 1949, gold sodium thiosulfate was administered intravenously in 2.5- to 25-mg. doses, for a total of 293 mg. The lesions progressed. From Nov. 16 to Dec. 14, 1949, crude liver extract, 2 cc., was given intramuscularly weekly. The lesions became much worse. From Dec. 21, 1949, to March 1, 1950, she was given mixed tocopherols orally, 50 mg. three or four times a day. Spread of the lesions continued. From March 1 to Dec. 27, 1950, gold sodium thiosulfate was again given intravenously in a total dosage of 380 mg. New lesions appeared, and the old lesions were more inflamed. From Sept. 12 to 27, 1950, she was given two tablets of bismuth sodium triglycollamate ("bistrimate") three times a day. This medication was discontinued because of gingival irritation.

On Jan. 10, 1951, the blood count was normal; the erythrocyte sedimentation rate had dropped from 37 mm. in August, 1950, and 33 mm. in December, to 16 mm. The patient felt well, but, despite gold therapy, the lesions were spreading, the new ones appearing on the chest. From Jan. 10 the patient was given tablets of methyltestosterone sublingually, starting with 10 mg. daily and increasing to 40 mg. daily in two weeks. This dose was maintained for three weeks and then decreased to 30 mg. a day for the next five weeks. Improvement was remarkable, with disappearance of all new lesions. The chronic discoid patches also began to fade, and the shoulder lesion was not tender for the first time in years. However, since there have been no menses since Jan. 13, 1951, the dose of testosterone has been decreased and now is 5 mg. daily. No masculinizing signs have been detected. The total dose of testosterone has been 2,300 mg. sublingually.

DISCUSSION

DR. E. T. BERNSTEIN: I have under observation two patients who responded beautifully to testosterone therapy. I suggest that this condition be called disseminated chronic discoid lupus erythematosus.

DR. SAMUEL M. KAUFMAN: At the last meeting I mentioned a case of disseminated discoid lupus erythematosus treated with testosterone in a woman aged 44, involving the bridge of the nose and the cheeks under the eyelids. The patient received six intramuscular injections of 25 mg. of testosterone daily, followed by six intramuscular injections every other day. After an interval of two weeks, the patient resumed treatment, receiving again 6 injections of 25 mg. daily, followed by 6 injections every other day, a total of 24 injections. After this, the lesions flattened out and took on a bluish color. The eruption has not entirely cleared, however. I have not observed any characteristic changes or any hypertrichosis in the patient. I believe this form of therapy is beneficial, as most of the cases of lupus erythematosus are found in women.

DR. SAMUEL M. PECK: Dr. Rothman has suggested that in acute lupus erythematosus x-ray sterilization of the female was a life-saving procedure. This, of course, was before the days of cortisone and corticotropin (ACTH). If my memory serves me correctly, testosterone therapy

did not take the place of this sterilization procedure. This patient seems improved, but I have seen as much improvement with administration of vitamin E.

Dr. Joseph I. Singer (by invitation), Bay Shore, N. Y.: We had tried practically every other type of medication, including fairly large amounts of gold, vitamin E, and bismuth preparations, with failure to stop progression. Only since methyltestosterone has been administered have new lesions failed to appear, and the patient has lost all signs of inflammation in the lesions. We will probably have to stop testosterone administration at this stage, because she has reached about the maximum amount for a woman at any one time.

Nevocarcinoma (Melanoma) of the Foot. Presented by Dr. Royal M. Montgomery.
Subcutaneous Fat Necrosis of the Newborn. Presented by Dr. S. Irgang.
Vitamin A Deficiency of the Skin with Generalized Avitaminosis. Presented by Dr. Thomas N. Graham.
Case for Diagnosis: Pityriasis Rubra Pilaris? Presented by Dr. S. Irgang.
Plantar Radiodermatitis with Ulceration Treated by Plastic Repair. Presented by Dr. Royal M. Montgomery.

NEW YORK DERMATOLOGICAL SOCIETY

J. Gardner Hopkins, M.D.,† *President*
Anthony C. Cipollaro, M.D., *Secretary*
April 24, 1951

Anaplastic Epithelioma. Presented by Dr. Frank C. Combes.

T. W., a woman aged 68, first noticed some itching in the vulval region two years ago. The exact location cannot at this time be determined but a cutaneous eruption appeared which gradually extended to involve most of the anogenital region. The pruritus later gave way in part to pain and soreness. Several x-ray treatments were given but seemed to increase the pain. The patient had a complete mastectomy on the left for cancer one year ago. The patient was first seen by me on March 21, 1951, with a mammillated, bright beefy red, granulomatous, precisely defined lesion which extended from the pubis posteriorly to the anus and laterally into either crural fold. The surrounding skin is of normal appearance. The entire lesion is moist and glistening. At many sites the tips of the mammillated papillae are pearl-white. There is no evidence of deep infiltration on palpation at the borders. No regional lymph nodes are palpable.

The histologic study, while showing some features of benign familial pemphigus and Bowen's disease, conforms more with anaplastic epithelioma. Some features suggest Paget's disease.

DISCUSSION

Dr. George C. Andrews: Although the picture clinically looks like the one in the textbook, it doesn't seem to me that the histologic pictures in the book are like the slide I looked at; the lesion is now more characteristic of an epithelioma than of Paget's disease. Under the microscope it seemed a very uniform, well-organized type of tumor composed of cells which might be sweat-gland cells, with origin in an apocrine gland. It is certainly a well-differentiated and well-organized tumor which one would not expect to be radiosensitive. One cannot judge entirely from the histologic picture, but we do not expect a nevoid type of tumor, as a trichoepithelioma, to be radiosensitive. I don't think it is a trichoepithelioma but did think of a sweat-gland tumor. The deep involvement into the introitus would make it a difficult problem for roentgen-ray treatment. I will be interested in seeing the result of therapy.

Dr. Paul E. Bechet, Elizabeth, N. J.: There is considerable difference in the appearance of the lesion in the textbook and that of the lesion in the patient, who exhibits a sharply outlined, cauliflower-like, moist, raised, highly vascularized growth, whereas the plate showed a much flatter lesion, with nodules extending beyond its periphery. Clinically, the lesion strongly resembled an extramammary Paget's disease, which has often been reported, especially on the scrotum, penis, buttocks, and vulva. In a few instances even Paget cells have been present. Yet, in discussing a patient I presented with the diagnosis of extramammary Paget's disease, the late Dr. Frank Fraser refused to accept the diagnosis because the lesion was not located on the nipple areas. I should appreciate discussion on this subject.

Dr. Anthony C. Cipollaro: We have to accept the histologic diagnosis of some type of neoplasm. Whether it be Paget's disease, the intraepidermic type, or the anaplastic type, it is a neoplastic process. It is a low-grade malignant growth because it is an extensive process

† Dr. Hopkins died on Feb. 27, 1951.

with a great deal of vegetation and no glandular involvement. The patient is 68 years old, and I don't know whether I should favor doing a surgical procedure. She would have to have general anesthesia, and it would be a mutilating operation. I don't think anything will be lost by treating with irradiation. A dose of about 5,000 r over a period of three or four weeks may cause involution. If that should fail, we could always resort to surgery.

DR. LESLIE P. BARKER: Clinically this lesion is an epithelioma. Because of the amount of involvement of the vagina, I think it should be removed surgically.

DR. WILBERT SACHS: I agree with Dr. Fraser in that I, too, don't believe in extramammary Paget's disease, but in the light of anaplastic epithelioma I can't see what difference that makes, because I think nevocarcinoma, Paget's disease, Bowen's disease, and anaplastic epitheliomas are all forms of a similar process. The malignant tendencies of these growths depend on the amount of anaplasia, the extent the cells are changed, and the proportion of normal to abnormal cells. If the percentage is great as far as anaplasia is concerned, the malignant potentiality is great. I don't think it matters whether you call it Bowen's disease, Paget's disease, or anaplastic epithelioma. This picture is what it is—without looking at the slide—because of the degree of secondary infection, giving the cauliflower appearance. I should be inclined to agree to surgery rather than to irradiation.

DR. FRANK E. CORMIA: I should be inclined to agree with Dr. Cipollaro that, because of the relative chronicity and the age of the patient, treatment should be conservative. I should start with irradiation, and then use a more radical procedure if this should be a failure. I have always been confused regarding Paget's disease, because at times the lesion may be confined to the epidermis and characterized by a dyskeratotic process which may occur alone or with an underlying glandular type of carcinoma. In some cases the process is solely dyskeratotic and confined to the epidermis, notably in extramammary Paget's disease.

DR. MAURICE J. COSTELLO: This growth may be benign, but it has spread very rapidly. I believe removal by surgical measures would give the patient the best chance of cure. That type of operation will be followed by less suffering. If the patient should have a severe reaction from irradition, it would just make things harder.

DR. J. LOWRY MILLER: I should agree with treatment using either surgery or electrocautery. It is a large area for plastic surgery. I am against x-ray irradiation because I think it would be ineffective.

DR. FRANK C. COMBES: I have considered all suggested methods of therapy and have favored some operative procedure. The patient has had some superficial irradiation therapy but with no success. Of course, the dose did not approach 5,000 r. It never impressed me that this was a particularly radiosensitive lesion. Electrocautery would be followed by a lot of pain. I think small areas could be done at each session. The patient has a lot of secondary infection, which explains the vegetative nature of the lesion. One objection to roentgen therapy is that if it is unsuccessful difficulty might be encountered if subsequent plastic surgery were attempted.

Case for Diagnosis: Erythema Multiforme Bullosum? Ectodermosis Erosiva Pluriorificialis? Presented by DR. ANTHONY C. CIPOLLARO.

Case for Diagnosis: Atopic Eczema? Prurigo? Presented by DR. GEORGE M. LEWIS.

Case for Diagnosis: Scleroderma Associated with Arthritic Symptoms? Lupus Erythematosus? Presented by DR. LESLIE P. BARKER.

Case for Diagnosis: Chloasma? Presented by DR. J. LOWRY MILLER.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Edward F. Corson, M.D., *Chairman*

H. E. Twining, M.D., *Secretary*

April 20, 1951

Trichophyton Sulfureum Infection in One Adult and Two Children of a Family. Presented by DR. JOHN P. SCULLY, Reading.

A mother and two daughters, aged 4 and 7 years respectively, were affected. The mother first noted patchy scaling areas of the scalp of the elder girl more than a year ago, and a diagnosis of ringworm was made by a general practitioner. I examined the patient in May, 1950, and on two subsequent occasions and called the process "seborrhea." In March, 1951, both

children were examined again. The older child's picture had not changed. The 4-year-old child presented a scaling of the central area of the scalp and scarcity of hair, some broken off, suggesting trichotillomania. Examination under Wood's light always showed a normal condition. The mother has since exhibited a low-grade inflammatory plaque below the right clavicle, from which Trichophyton sulfureum was cultured. The elder child has recently displayed a low-grade inflammatory reaction in the scaling plaques. The condition of the younger child is unchanged.

McManus stain and cultures revealed Trichophyton sulfureum.

DISCUSSION

DR. DONALD M. PILLSBURY: I have followed the work of Seale and others in the Southwest and recently had a letter from Dr. Livingood, of Galveston, Texas, and it is apparent that this type of infection is spreading rapidly throughout that area. We see an occasional case here, and it is Dr. Livingood's opinion that this condition is obviously going to be the tinea capitis problem of the future. One of the great difficulties is that we cannot recognize these cases in routine examination under the Wood light, and we may be faced with the problem of producing temporary epilation in adults by roentgen rays.

DR. FRED D. WEIDMAN: It is axiomatic in mycology that the styles change from year to year and from generation to generation in respect to the predominating fungus. In my early experience tinea cruris was due almost invariably to Epidermophyton; now it is caused by Trichophyton mentagrophytes. In Germany, Trichophyton rosaceum was the main cause of ringworm of the beard; a few years later, this species had disappeared almost entirely. Everywhere, Trichophyton mentagrophytes infection of the toes was rather unusual; at that time Epidermophyton floccosum infection predominated. We are experiencing a repetition of this in respect to these scalp cases. Dr. Louis Pipkin, of San Antonio, Texas, told me of the large number of Trichophyton sulfureum cases that they see there. Of course, in Mexico City, Mexico, almost 90% of all cases of scalp ringworm are due to Trichophyton. I agree with Dr. Pillsbury that we are going to see more Trichophyton sulfureum infections in the Philadelphia area.

DR. JOHN P. SCULLY, Reading: I should like to know if these children should undergo x-ray epilation.

DR. DONALD M. PILLSBURY: Seale's criterion for epilation versus local treatment is the same as the one generally applicable in Microsporum audouini infection; namely, if there is inflammatory reaction, probably spontaneous cure, with some help from a fungicide, will occur. But if, over a long period, there is no evidence of local inflammatory response—probably immune response—epilation is indicated. It seems to me that these children will not be cured by local therapy.

Keratosis Follicularis (Darier's Disease) Treated with Grenz Rays. Presented by DR. HARVEY BLANK.

S. G., a healthy, robust white man, aged 31 years, presents typical hyperkeratotic, yellowish-red papules which have become confluent in several areas. They are profuse on the face, chest, and back and in the gluteal cleft, with patches on the arms and elsewhere. The lesions between the buttocks and behind the ears are forming vegetations.

The patient has been presented before the Philadelphia Dermatological Society in the past as showing typical slowly progressive keratosis follicularis (Darier's disease). He is presented now to show the results of grenz-ray therapy in this disease.

On the accompanying diagrams a number of sharply shielded square areas of the body are indicated on which the patient received grenz-ray therapy. The dates and dosages are indicated. From inspection of the treated areas, I believe that the following conclusions may be drawn: 1. Grenz rays will cause clearing of typical areas of keratosis follicularis. 2. The thick nodular papules do not respond as well as the more superficial lesions. 3. Irradiation of sufficient kilovoltage in one dose, producing a marked erythema with weeping and crusting and subsequent involution of lesions, does not produce permanent epilation of ordinary or lanugo hair. 4. With sufficient irradiation (1,000 r in one dose) there does not seem to be any appreciable recurrence

in areas treated more than one year ago. 5. An erythema dose of ultraviolet irradiation failed to cause a flare of a test patch of previously untreated lesions. The factors used in the grenz-ray therapy were: beryllium window tube, 15 kv., 15 ma., 20 cm. skin test dose, half-value layer 0.038 mm. Al; 1,000 r delivered in 2 minutes 36 seconds. In addition, this patient received water-soluble vitamin A1 ("aquasol-A") by intramuscular injection, 50,000 units each, 17 injections from Jan. 5 to Feb. 16, 1951, combined with thyroid extract, 1 grain (0.06 gm.) daily. No appreciable effect was noted from this therapy. The patient had previously received vitamin A in oil orally and intramuscularly with no benefit.

DISCUSSION

DR. FRED D. WEIDMAN: Why has she not received additional therapy?

DR. HARVEY BLANK: We were anxious to wait at least one year following this therapy to see if any telangiectasia, marked atrophy, or any other symptoms would develop as late x-ray changes before we proceeded. A marked inflammatory reaction develops with weeping and crusting at the site of therapy when one gives 1,000 r. Dr. Cipollaro commented very adversely on this therapy at the Atlantic Dermatological Conference and felt that not only would it fail but it would cause an aggravation because all forms of radiation therapy, in his opinion, produced an exacerbation, and there was considerable agreement with him. Therefore, we have been rather hesitant to proceed.

DR. DONALD M. PILLSBURY: We should not speak too loosely about grenz-ray therapy. This treatment was given with 15 kv., with beryllium widow without filter, and Bucky believes that this is about what should be considered in the grenz-ray range. Perhaps as we use other kilovoltage with varying depths of penetration, we may find that some of the lower voltages are quite useful. We have treated a fair number of port-wine stains with moderately good results. The highest dosage we have used with 15 kv. is 7,500 r, and that was over an entire forearm. In treating the lesions on the face and the lower part of the back of this man, it might be advisable to divide the dose somewhat—possibly 250 or 300 r at a time at intervals of two or three weeks. I am not sure that the cumulative effect will be as good as the sharp reaction produced by 1,000 r. In the treatment of small, superficial epitheliomas we frequently give 2,000 r. I am sure that this man will not have any adverse effect with this amount of irradiation; it does not penetrate the deep vascular bed.

Syphilis, Late, Mutilans, Trophic or Endarteritic in Origin, as Opposed to Classic Gumma. Presented by CAPTAIN ROBERT L. GILMAN (MC), U. S. N.

B. H. P., a white man aged 55 years, who saw service only in this country in World War I, presents almost complete amputation of the midright hand. The index finger stub still persists. Two metacarpals are missing. The skin is atrophic, occasionally crusted, with no sinuses and no draining at present. The patient is vague about the history of the illness. The onset was about 20 years ago, probably as "boils" on the flexural surface of the right wrist, with slow extension, the fingers being involved peripherally with the process reversing up the hand. There have been occasional open lesions.

The patient is tall and spare, weighing 160 lb. (72.6 kg.). He has had petit mal for the past five years, for which he has been given small doses of diphenylhydantoin (dilantin®) sodium and phenobarbital. He has lost 55 lb. (24.9 kg.) in the past 10 years. He has a good appetite and feels exceptionally well since recent syphilitic therapy.

A roentgenogram of the chest was normal. Results of all urinalyses have been within normal limits. Repeated serologic tests for syphilis showed 444 Kahn units and a positive Kolmer reaction. A cerebrospinal fluid examination revealed 4 cells, 64 mg. of protein per 100 cc., a negative reaction to the serologic test for syphilis, and a flat colloidal gold curve.

The patient has had considerable (and excessive) local applications to the hand. The last was daily applications of ammoniated mercury ointment for the past six months. This was changed to cleansing measures and application of boric acid ointment. Syphilitic therapy since Dec. 20, 1950, has consisted of administration of saturated solution of potassium iodide, 25 drops three times daily, and weekly intramuscular injections of bismuth subsalicylate to a total of 14 injections. Improvement has been marked.

DISCUSSION

DR. VAUGHN C. GARNER: For many years Dr. John Stokes taught that three questions should suggest themselves when the physician is confronted with bizarre cutaneous conditions: Can this be syphilis? Can it be due to drugs? Can it be factitial? I should like to ask Dr. Gilman if he is convinced that there is not a self-mutilating factor involved in this case. Even for syphilis, this is so bizarre that it is difficult, in spite of the response to antisyphilitic treatment, to accept that diagnosis without at least some question.

DR. IRA L. SCHAMBERG: Dr. Gilman is to be commended for carrying out the therapeutic test with bismuth rather than with penicillin.

DR. FRED D. WEIDMAN: Can this be syringomyelia?

CAPTAIN ROBERT L. GILMAN (MC), U. S. N.: This patient came into the hospital late in November. He is well educated and has engaged in various occupations, including those of concert pianist and sales manager personnel work; he is now at the United States Naval Base. He was sent to the hospital for diagnosis, and my impression for a time was that he had a factitial dermatitis. I took photographs to the meeting of the American Academy of Dermatology and Syphilology, and many members agreed that the factitial explanation was certainly to be considered. You will note from the history that in the last six months he has used nothing but ammoniated mercury. Syphilis, syringomyelia, leprosy, epidermolysis bullosa, and cancer were all considered, but still the factitial idea predominated. We were unable, however, to determine how it could be accomplished. There is nothing in the roentgenogram to suggest any specific granuloma. As to syringomyelia, a year and a half ago he was studied very thoroughly in one of the clinics in the city and was examined by a prominent neurosurgeon, and the gist of the whole thing, including the petit mal which has been present for the past five years, is that no diagnosis was made. The serologic tests for syphilis were performed as a matter of routine, and reactions were reported completely positive in both complement-fixation and precipitation tests. Three more tests seemed to confirm the diagnosis, and antisyphilitic treatment was begun. The spinal fluid was normal. I could not conceive of the picture as being fundamentally clinically or pathologically gumma. It started originally in the flexural tendons of the right wrist. The invasion advanced; the wrist opened, and I have postulated that the vessels in his wrist were involved at that time, the only way in which we can explain the disease going from the wrist to the finger tips and back up the hand. I believe he had an endarteritis and then some type of atrophy. We were never able to find an area from which we could get any good biopsy material. At no time were there any sinuses or pus from which we could obtain cultures. Therefore, we have tentatively decided, because of the improvement since using bismuth and potassium iodide, that it is syphilis. I have not wholly abandoned the idea that there is still a factitial element.

FOLLOW-UP NOTE, JULY 15, 1951.—After the presentation of this patient at the April meeting, his wife has assured me that she is convinced that a considerable portion of his difficulty has been due to the tight, constricting bandages and dressings which he previously used. If this is so, the factitial element assumes a much more reasonable part in the whole process. He has gained 15 lb. (6.8 kg.) in weight. He is disinclined to avail himself of plastic surgery to obtain a better result.

Erythrodermic Mycosis Fungoides Associated with Leukemia. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. FREDERICK URBACH, Elkins Park.

Case for Diagnosis: Tuberculosis? Presented by DR. JOHN M. SIEGEL, Allentown.

Xanthoma Tuberosum with Cardiac Manifestations Improved by Low-Fat Diet. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. FREDERICK URBACH, Elkins Park.

Onychomycosis and Dermatophytosis. Presented by DR. JOHN P. SCULLY, Reading.

Sarcoid. Presented by DR. STEPHEN T. WHELAN, Upper Darby, and (by invitation) DR. JOHN LASKAS.

Arsenical Keratoses. Presented by DR. JOHN P. SCULLY, Reading.

Contact Dermatitis Due to Mercury (Thimerosal [Merthiolate]). Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. CARL Z. BERRY JR.

Keratosis Pilaris (Avitaminosis A). Presented by DR. HENRY HARRIS PERLMAN.

Localized Hypertrichosis. Presented by DR. HENRY HARRIS PERLMAN.

Canities (Acquired), Partial Hereditary (Poliosis). Presented by CAPTAIN ROBERT L. GILMAN (MC), U.S.N., and DR. HENRY HARRIS PERLMAN.

Hypertrophic Lichen Planus; Keratosis Palmaris (in Cutem Penetrans, Arnold or Kyrle). Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. C. JACOBSON.

Keratosis Palmaris (in Cutem Penetrans, Arnold or Kyrle). Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. FREDERICK URBACH, Elkins Park.

Xanthoma Tuberosum with Thromboangiitis Obliterans. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. Frederick Urbach, Elkins Park.
Xanthoma Tuberosum Markedly Improved by Low-Fat Diet. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. Frederick Urbach, Elkins Park.
Biliary Cirrhosis; Xanthomatosis. Presented by Dr. Carroll F. Burgoon and (by invitation) Dr. Charles M. Thompson.
Nevoxanthoendothelioma. Presented by Dr. Vaughn C. Garner and (by invitation) Dr. Frederick Urbach, Elkins Park.
Case for Diagnosis: Porphyria? Presented by Dr. Harvey Blank and (by invitation) Dr. Frederick Urbach, Elkins Park.
Incontinentia Pigmenti. Presented by Dr. Harvey Blank and (by invitation) Dr. C. Jacobson.
Poikiloderma Atrophicans Vasculare with Associated Scleroderma or Dermatomyositis. Presented (by invitation) by Lieutenant J. F. Morrell (MC), U.S.N., and Lieutenant (jg) J. J. Downey (MC), U.S.N.
Necrobiosis Lipoidica Diabeticorum. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. M. A Haanes.
Alopecia Universalis with Dystrophic Nail Changes. Presented by Dr. Carroll F. Burgoon.
Case for Diagnosis. Presented by Lieutenant J. F. Morrell (MC), U.S.N. (by invitation).
Periarteritis Nodosa. Presented by Dr. John P. Scully, Reading.
Pseudoxanthoma Elasticum. Presented by Dr. Stephen T. Whelan, Upper Darby, and (by invitation) Dr. John Laskas.

H. E. Twining, M.D., *Chairman*

Bertram Shaffer, M.D., *Secretary*
Sept. 21, 1951

Dermatitis Herpetiformis. Presented by Dr. Reuben Friedman and (by invitation) Dr. Jack Weiner, Dr. Joseph Gropen, and Dr. C. J. D. Zarafonetis.

N. L., a white woman aged 55 years, presents a generalized polymorphic eruption composed of discrete and grouped vesicles and bullae, crusted and eroded lesions, pigmented areas, and some scars, involving chiefly the face, neck, sternal and interscapular areas, sacrum, and extremities.

The eruption appeared in April, 1950, with severe pruritus, especially marked at night. With the diagnosis of dermatitis herpetiformis, treatment was started with sulfapyridine, 0.5 gm. four times daily; tripelennamine (pyribenzamine®) hydrochloride, 50 mg. four times daily, and tar baths at bedtime. There was spectacular improvement, but treatment was stopped in September, 1950, when she was hospitalized for agranulocytosis, with a white blood cell count of 950 per cubic millimeter. Within two weeks the eruption recurred. Sulfadiazine, 0.5 gm. daily, was tried, but on the second day, after a total of two tablets, the white blood cell count dropped to 3,600 per cubic millimeter, and this treatment was discontinued. Penicillin, terramycin, vitamin B_{12}, nicotinic acid, tripelennamine, and progesterone were ineffective. Potassium arsenite (Fowler's) solution appeared to be variable in its action. On Aug. 21, 1951, administration of *p*-aminobenzoic acid, 3 gm. every three hours, was started. There was an initial flare in the first few days, but the patient now states that her pruritus is improved, although the eruption is virtually the same.

DISCUSSION

Dr. C. J. D. Zarafonetis (by invitation): I should like to emphasize at the outset that we are not advocating *p*-aminobenzoic acid as a replacement for all the other pharmaceuticals in the dermatologic armamentarium. We are giving this patient *p*-aminobenzoic acid because of our experience with a relatively large series of patients with dermatitis herpetiformis who have responded to it. In this particular patient, while her condition can be controlled with sulfapyridine therapy, agranulocytosis develops very quickly with ingestion of small quantities of the drug. It is too early to judge the effects of *p*-aminobenzoic acid, since she has been using it only a few weeks. The sequence of events which led us to try *p*-aminobenzoic acid in dermatitis herpetiformis was as follows: We first used *p*-aminobenzoic acid in therapy of the rickettsial infections. The sulfonamides did not improve these diseases but made them worse. Therefore, Dr. Snyder, of the Rockefeller Institute, New York, decided that if a sulfonamide antimetabolite was present it might be effective in typhus, scrub typhus (tsutsugamushi fever), and Rocky Mountain spotted fever. As we studied *p*-aminobenzoic acid, one of the first things we learned was that it apparently works by increasing intracellular metabolism. For that reason, we felt that it was justifiable to use it in leukemia, since the cells were metabolizing abnormally and with a substratum of *p*-aminobenzoic acid they would not be able to adapt themselves. In myelogenous leukemia one can readily bring down the white blood cell count with large doses

of *p*-aminobenzoic acid. At this juncture I approached Dr. Curtis. Starting with patients having lymphoblastoma cutis, many of whom have responded either partially or completely to the administration of *p*-aminobenzoic acid over a prolonged period, we have treated 75 patients with all types of lupus erythematosus, and the results have been mixed. In dermatomyositis and scleroderma I prefer to use *p*-aminobenzoic acid to any other form of treatment. We were all concerned with the sunlight sensitivity factor. There was a patient with severe dermatitis herpetiformis who had responded to sulfapyridine but who was showing bone-marrow depression. She was sent to Florida but did not respond to the climate. When she came back we asked her if the sunlight had made any difference in her lesions. She said she thought they were more pruritic and more irritating when she was in the sun. We treated her with *p*-aminobenzoic acid. Within two weeks she improved greatly, and it was not long before the lesions were completely cleared. I do not mean to imply that *p*-aminobenzoic acid should be used when other means are effective, but it is a drug one can use with safety if it is given in sufficient dosage. The only thing to be watched for is spontaneous hypoglycemia, which may develop if the patient does not eat well. All of you are aware of the synergism between *p*-aminobenzoic acid and cortisone; study of the synergism between corticotropin and cortisone (such possibilities of synergism between the two compounds are certainly to be investigated) shows that conditions which respond to one or the other may respond to both without toxicity. Thus, we may have good suppressive therapy in the near future.

DR. MEYER L. NIEDELMAN: Has Dr. Zarafonetis used nicotinic acid in dermatitis herpetiformis? It is known that both nicotinic acid and *p*-aminobenzoic acid have the pyridine radical which is felt to be responsible for their therapeutic value.

DR. C. J. D. ZARAFONETIS (by invitation): One of my patients receiving *p*-aminobenzoic acid was given nicotinic acid, and the eruption flared immediately. Dr. Curtis had the same experience with reversal of the order of the drugs. One must beware of previous therapy when trying a second substance. We have observed, and we are trying to prove objectively, that if a patient has been receiving an arsenical preparation or a gold compound, particularly a patient with one of the lupus group, and is given *p*-aminobenzoic acid, the eruption will flare up in the first few days. However, if *p*-aminobenzoic acid therapy is continued, within a few weeks he will improve. One thus releases the previous suppressive effect of the gold compound or other drug. I feel this is a very important point; we are apt to discard a new treatment simply because we ignored what went before. It also helps one to realize the tissue level of this activity.

Creeping Eruption. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. WILLIAM SNYDER.

Adenoma Sebaceum with Typical Triad of Epiloia (Pringle's Syndrome; Tuberous Sclerosis). Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. JACK WEINER and DR. ADOLPH BLEIER, Chester.

Partial Permanent Alopecia Following Roentgen-Ray Therapy for Tinea Capitis, Depigmentation, Verrucae. Presented by DR. MEYER L. NIEDELMAN and DR. ADOLPH BLEIER, Chester.

Case for Diagnosis: Lupus Erythematosus? Presented by DR. LEWIS M. JOHNSON, Lancaster.

Pemphigus Erythematosus (Senear-Usher Syndrome). Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. JACK WEINER, DR. JOSEPH GROPEN, and DR. C. J. D. ZARAFONETIS.

Generalized Neurodermatitis (Atopic); Atopic Cataract, Left Eye; Dermatopathic Lymphadenitis (Lipomelanotic Reticulosis). Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER.

Keratosis Pilaris. Presented by DR. BERNARD L. KAHN.

Sulzberger-Garbe Disease; Dermatitis Herpetiformis. Presented by DR. H. E. TWINING and (by invitation) DR. J. R. COX.

Case for Diagnosis. Presented by DR. H. E. TWINING and (by invitation) CAPTAIN W. N. NEW (MC), U.S.N.

Acrosclerosis and Scleroderma. Presented by DR. CARROLL S. WRIGHT, DR. REUBEN FRIEDMAN, and (by invitation) DR. JACK WEINER.

Mycosis Fungoides. Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER.

Squamous-Cell Cancer of the Penis. Presented by DR. MEYER L. NIEDELMAN.

Case for Diagnosis: Parapsoriasis? Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER and DR. JOSEPH GROPEN.

Dermatitis Herpetiformis; Bullous Form of Erythema Multiforme. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. M. C. WESTPHAL.

Creeping Eruption. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. WILLIAM SNYDER.

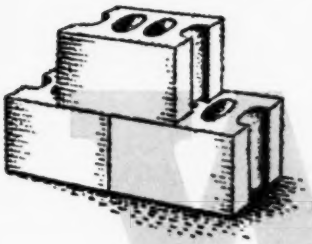
Chronic Folliculitis and Perifolliculitis (Acnitis?); Seborrheic Dermatitis of the Scalp. Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER.

Parapsoriasis. Presented by DR. CARROLL S. WRIGHT, DR. REUBEN FRIEDMAN, and (by invitation) DR. JACK WEINER.

Keratosis Follicularis (Darier's Disease). Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. JACK WEINER.

Keratosis Follicularis (Darier's Disease), Right Submammary Region; Nonspecific Dermatitis, Chest Wall. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. JACK WEINER and DR. JOSEPH GROPEN.

Pemphigus Erythematosus. Presented by DR. CARROLL S. WRIGHT and (by invitation) DR. JOHN B. ROXBY and DR. DONALD N. TSCHAN.



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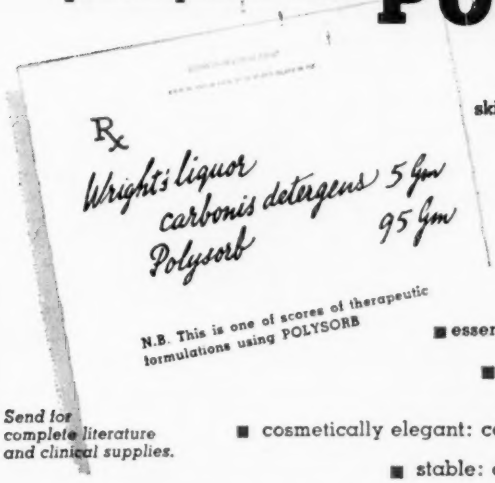
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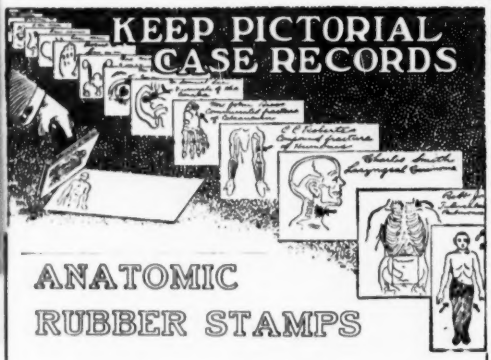

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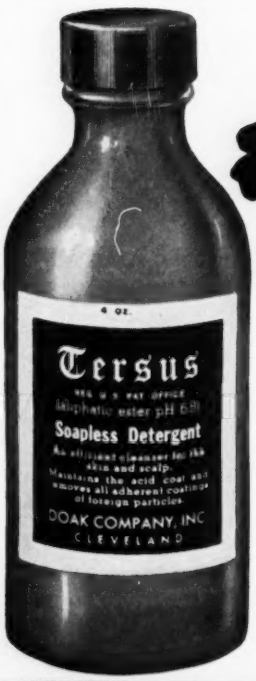

Tersus

* SOAPLESS DETERGENT

An efficient cleanser—

for the hands and scalp

Maintains the acid coat and removes all adherent coatings of foreign particles. Aliphatic ester pH6.8, which is slightly acid. Does not contain any free fatty acids or alkalis.

Recommended for use in cases where soap has a tendency to cause dermatitis or aggravate skin disorders . . . does not form the precipitation of calcium soaps.

Tersus has been clinically tested by dermatologists and is considered to be comparatively free from irritating qualities.

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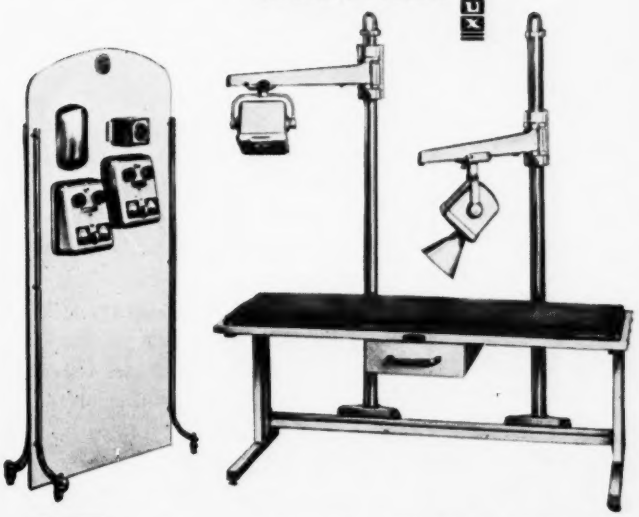
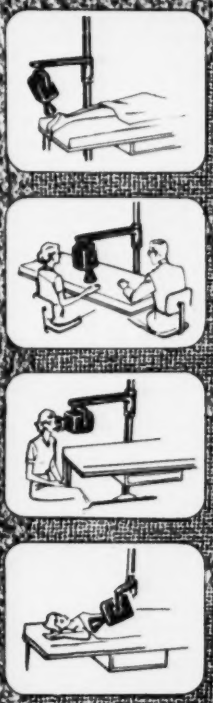
now GRENZ or X-RAY

With The NEW "DUPLEX TREATMASTER"

by *Universal*





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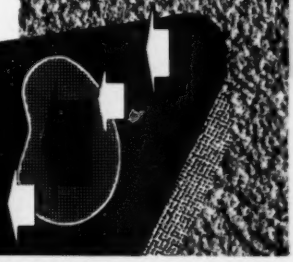
SIMPLE TO OPERATE— Extremely flexible . . . operates on ordinary 115-volt A.C. line.

COMPACT— Requires space of ordinary table. Available in combination as shown, or as single X-ray or Grenz Ray units.

THE FINEST SUPERFICIAL X-RAY THERAPY OF ITS KIND



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suspensoid vehicle

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CROLEUM SUSPENSOID VEHICLE is a colloidal emulsion used to compound topical applicant prescriptions and as a non-irritating dermal emollient without added medication. It has the following characteristics:

Creamy, opaque, white semi-fluid—flows readily. Dispersible in water or aqueous body exudates. Spreads instantly on wet or dry treated areas. Non-irritating, non-staining, non-drying. Penetrates actively into tiny dermal crevices. Easy to apply—pour, swab, spread or spray. Excellent dermal emollient and massage lubricant. Compatible with most used topical drugs. Forms no impenetrable grease films. Pleasant odor, pH 6.6-6.8

What It Is For . . .

CROLEUM Vehicle is an excellent base in which to compound prescribed topical drugs. Pour desired quantity of CROLEUM Vehicle into glass or porcelain mortar and blend in the prescribed medications with pestle (non-metallic). CROLEUM Vehicle will dissolve aqueous or oil soluble drugs. Insoluble drugs or amounts in excess of saturation level will remain suspended in the carrier over wide temperature variations.

CROLEUM Vehicle without added medication is an excellent non-irritating, low cost, dermal emollient and detergent. It finds many hospital uses as an effective massage lubricant, skin cleanser and general purpose skin lotion. Dilute with distilled water if thinner consistency is desired.

How Administered . . .

CROLEUM is non-drying and flows readily. Apply to skin with spray, swab or sponge—flow it on—spread with sterile tongue blade—or dilute with sterile distilled water (50%) and spray. Use also as a wet dressing or pack. Dressings will seldom adhere to CROLEUM treated surfaces.

What It Does . . .

While this is determined by the added medicament and its strength, CROLEUM prepared prescriptions of low drug concentration may produce therapeutic results not surpassed by larger amounts in ordinary grease bases. No grease films are formed. CROLEUM with added medication actively penetrates incrustations and small dermal crevices and thus provides intimate medication contact in otherwise inaccessible places.

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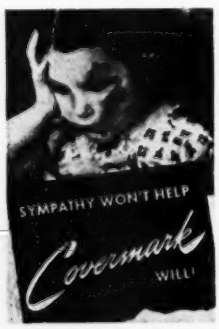
A unique preparation, COVERMARK is highly recommended by hundreds of doctors and dermatologists for the concealment of permanent and temporary facial and skin disfigurations. Called a "modern miracle" by Reader's Digest, COVERMARK conceals *birthmarks, burns, scar tissue, vitiligo, broken veins* and *discoloration* around the eyes or on the body.



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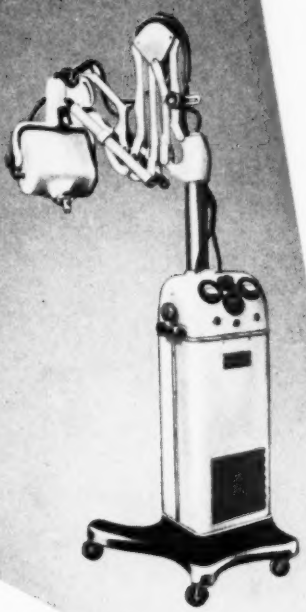

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